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ADENOMA OF ISLET CELLS WITH HYPERINSULINISM

A REVIEW

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THE literature on the internal secretion of the pancreas has now reached such tremendous proportions that it practically defies review. The subject of this paper, however, cannot be approached with any understanding without a glance backward at the steps which have led us to our present knowledge. Spontaneous hyperinsulinism, of which we now speak almost lightly, is, as a matter of fact, only ten years old, and could not possibly be understood without the painstaking studies of its antithesis, hyposecretion. This phenomenon, veiled for years in the obscurity of the disease diabetes mellitus, has fascinated generations of our predecessors. Only a profound scholar would dare attempt to trace the earliest history of the disease, but there are, in easily available sources, data which, if studied chronologically, make a most dramatic sequence. Correctly they should be listed in order, but for a time at least they were divided into two groups, the findings of those interested primarily in anatomy and histology, and of those interested in physiology and disease. The lines of thought are somewhat arbitrarily separated in the following table, which of necessity shows only the most outstanding features of the study (Table I).

HISTORIC REVIEW

The column under Histology is almost self-explanatory. After Langerhans[86] first described the islands which Laguesse[83] named after their discoverer, little was done until Kühne and Lea,[78] in 1882, described the capillary network in which lie the island cells. Then Lewaschew,[91] in 1886, made a very scholarly study of stimulation by overfeeding or with pilocarpine. Unfortunately, he described cells which he considered intermediate between acinar and islet cells, and he therefore interpreted the islets as functionally exhausted acini. This led to great confusion, and for years retarded any general acceptance of the endocrine nature of these structures.

Beginning in 1893, and studying and publishing with unabated vigor for twenty years or more, Laguesse[82] added greatly to the subject. In

TABLE I

Chronologic Historic Data

HISTOLOGY	PHYSIOLOGY AND DISEASE	TUMORS	HYPERINSULINISM
	1788 Cawley: Calculi. Diabetes		
	1849 Bernard: Hypoglycemia		
1869 Langerhans: Islands			
1882 Kühne and Lea: Capillary net			
	1884 Arnozan: Ligation of duct in animals. No diabetes		
1886 Lewaschew: Islands exhausted acini			
	1890 v. Mering and Minkowski: Ablation produced diabetes		
	1892 v. Mering and Minkowski: Subcutaneous graft prevented diabetes		
	1892 Hédon and Thiroloix: Confirmed graft experiment		
1893 Laguesse: Granules. Endocrine?			
	1894 Hanseman: Saw fibrosis, *etc.*, in human diabetes		
1899 Diamare: Islands independent structures anatomically			
	1900 Ssobolew: Ligation of duct atrophy of acinar cells. Islands remained		
	1900 Schulze: Ligation of duct atrophy of acinar cells. Islands remained		
	1901 Opie: Hyaline degeneration of islands in diabetes		
		1902 Nicholls: Island tumor	
		1904 Ssobolew: Hypertrophy in diabetes	
		1905 Herxheimer: Hypertrophy in diabetes	
		1907 MacCallum: Hypertrophy in diabetes	
1908 Lane: Alpha and beta granular cells		1908 Morse: Two adenomata	
		1911 Cecil: Adenoma	
1912 Bensley: Vital staining. Duct origin. "C" cell nongranular	1912 Kirkbride: Lane stain on duct ligated specimens		
	1913 Homans and Allan: Hydropic degeneration of beta cells in overstimulation		
		1920 Dubreuil and Anderodias: Hypertrophied islands in newborn—diabetic mother	
	1922 Banting and Best: Insulin		1922 Banting: Insulin shock
	1923 Copp and Barclay: Restoration of exhausted beta cells after insulin administration		1923 Harris: "Hyperinsulinism"
1924 Bowie: Alpha, beta and gamma granular cells in teleost			
	1925 Boyd and Robinson: Regeneration of islands in insulin treated cases	1925 Lang: Adenomatosis	
		1926 Gray and Feemster: Confirmed Dubreuil	
		1926 Warren: Collected 20 cases	
			1927 Wilder: Island cell carcinoma with hyperinsulinism
			1929 Howland: Island cell adenoma with hyperinsulinism surgically cured (Roscoe Graham)
	1930 O'Leary: Secretion islet cells *in vivo*		
1931 Bloom: Alpha, beta and delta granular cells in man			

Annals of Surgery June, 1933

1893, he described the histology, including granules in the island cells, and the capillary network, and suggested the possibility of internal secretion on purely anatomic grounds. Diamare,[37] in 1899, confirmed his findings. In 1902, Laguesse[83] also described in detail the histology of the preserved islands in the atrophied pancreas following ligation of the duct.

The next histologic advance was contributed by Lane[84] in his famous description of the staining technic by which he demonstrated two types of granule containing cells, and called them alpha and beta cells. Later Bensley,[13] in 1912, added to the technical procedure a vital staining method for counting the number of the islands, demonstrated the origin of both types of cells from duct epithelium, and not from acinar cells, and described a third nongranular cell "C". The amount of island tissue he found not so inconsiderable as the opponents of the endocrine school claimed, for he estimated that in the adult guinea-pig there were 56,000 islands. All this work is summarized in his Harvey lecture in 1915.

In 1924, Bowie[18] described alpha, beta and gamma granular cells in the teleost, and in 1931 Bloom[16] described alpha, beta and delta granular cells in man.

In the column under Physiology and Disease the first observation antedates the discovery of the islands by nearly a hundred years. In 1788, Cawley[28] described the finding of pancreatic calculi in a case of diabetes, and during the next hundred years it was gradually accepted that the pancreas might be related to diabetes. In 1849, Claude Bernard[14] published his famous monograph in which hyperglycemia and glycosuria are discussed.

Arnozan and Vaillard,[6] in 1884, showed that no diabetes ensued after ligation of the duct. They described the preserved islands but failed to realize their significance.

A long interval elapsed before v. Mering and Minkowski,[103] in 1890, published their famous experiment in which they showed that ablation of the pancreas in dogs, rabbits, and pigeons produced diabetes. Two years later they also completed a very significant and conclusive experiment, a successful subcutaneous graft of pancreas with subsequent extirpation of the remaining gland. The animal developed no glycosuria. Upon removal of the graft an extreme glycosuria developed, leading to death. This work was confirmed in the same year by two independent observers, Hédon[55] and Thiroloix.[151]

Shortly after this, in 1894, Hanseman[52] saw fibrosis and atrophy in the pancreas in 40 cases of diabetes.

At almost the same time (1895) Schäfer,[133] in a popular lecture, pointed to another bit of evidence for the internal secretion theory in that ablation caused death of the animal while a total pancreatic fistula did not. But it remained for two independent workers to make the crucial experiment which relegated this secretion definitely and finally to the islands.

Ssobolew[143] and Schulze,[135] working at practically the same time in 1900, both published experiments on ligation of the ducts. In the animals which survived there was atrophy of the organ as a whole but the islands remained preserved and the animals were not diabetic. In the same paper Ssobolew also records seeing changes in the islands in diabetes, and ends with a paragraph which, had its full import been realized, might have changed the history of medicine considerably. He says, "The future will show how far experiments in this direction will be crowned with success. Even now we may come nearer to the solution of the problem by making exact studies of the islands *in vitro* and *in vivo*. Formerly the entire pancreas was used for this purpose. Now, however, in ligation of the excretory duct we have a means of isolating the islands anatomically and of studying the chemistry of these cells separated from the digestive ferments.

"This anatomic isolation of the islands enables us also to try organotherapy on diabetes in a rational manner. All former attempts to cure diabetes by administering the whole pancreas in various ways have failed. Since it is difficult to secure in any quantity pancreas in which only the island tissue has been preserved, one can substitute pancreas of newborn animals—calves, for instance, in which the islands are well developed in comparison to the digestive apparatus. Moreover, the pancreas of the newborn is little capable of digestive activity and we may expect that its digestive juice will not interfere with the action of the substances secreted by the islands. At all events, we are justified in the hope that in the near future the question will be decided whether or not this method of approach will succeed in relieving the ills of the diabetic patient" (Doctor Laidlaw's translation).

Practically simultaneously, in a paper which seems to have had much wider circulation than Ssobolew's, possibly because his was originally a doctor's thesis published in Russian, Opie[114] recorded hyaline changes in the islands in diabetes. Kirkbride,[74] in 1912, applied Lane's stain to the atrophied portion after duct ligation, and showed granules in island cells. Homans[64] and Allan,[2] in a series of papers (1913–1915) showed changes in experimental diabetes confined to the beta cells of Lane. There followed extensive work on the pathology of diabetes, which cannot be reviewed here, but all of which was confirmatory evidence that disease of the islands led to hyposecretion of some substance necessary to carbohydrate metabolism, without which the patient suffered from hyperglycemia.

A decade followed in which the goal, finally reached by Banting and Best,[7] in 1922, was the aim of a host of eager and tireless investigators. Curiously enough, Banting's inspiration was a short historic review by Baron,[11] written in 1920 as part of an article which dealt chiefly with the relationship of pancreatic calculi to island damage. Recapitulating in their experiments the crucial investigations of the 30 years' work which we have just reviewed, they first obtained insulin, or "isletin," as they called it, from a Ringer solution extract of the pancreas of a dog in which

the duct had been ligated for ten weeks. Next they obtained it from the pancreas of fetal calves in which the proteolytic ferments were absent, and then they succeeded in extracting it from adult ox glands. So this was done! A year later, with insulin at hand, Copp and Barclay[30] repeated Homans' experiment and demonstrated restoration of exhausted beta cells by administration of the extract.

In 1925, a somewhat analogous finding was reported by Boyd and Robinson,[19] who presented evidence of regeneration of the islands in an insulin treated case of diabetes.

In 1930, O'Leary[112] studied islet cells in living animals (mice) and in response to introduction of dextrose saw vacuoles form and migrate to the periphery of the cell next the capillary, where they apparently diffused their contents.

It is almost an anticlimax to review the third column, the pathologists' study of localized hypertrophy or adenoma of island cells. The first is a single tumor reported by Nicholls[109] (1902) without clinical history. Ssobolew,[143] the prophetic scholar, in 1904 described an hypertrophied island in a postmortem on a diabetic. This measured 1.5 Mm. and the rest of the islands were markedly atrophic, but he described some areas of proliferation. In 1905, Herxheimer[59] confirmed this work by describing hypertrophy of the islands of five diabetics together with adenomata in one. MacCallum[95] confirmed the hypertrophy in 1907. In 1908, Morse[105] described two cases of adenoma, and in 1911, Cecil[29] reported another. There were other scattered observations, and probably many not published. As early as 1920, Dubreuil and Anderodias[39] reported hypertrophy of the islands in a newborn child of a diabetic mother, antedating Gray and Feemster's[50] better known article by six years. Lang[85] (1925) published the first case of multiple adenomata—adenomatosis.

Warren,[156] in 1926, reviewed 20 cases, four of his own. This paper stimulated great interest in island cell tumors, although the author did not suggest any possible physiologic significance.

A number of adenomata have been reported since but we must go back a little and examine the fourth column to find the impetus for the work. Here we see that nine months after the discovery of insulin Banting[9] and his associates perforce discovered something else. The dosage was still, naturally, not standardized and the phenomenon of hypoglycemia was dramatically called to their attention. This, they said, was characterized clinically by nervousness, tremulousness, hunger, weakness, sweating, pallor and flushing, anxiety, faintness, vertigo and diplopia, and in the more striking cases by excitement, emotional instability, sensory and motor aphasia, disarthria, delirium, disorientation, confusion, syncope or collapse, and unconsciousness. They did not mention convulsions. The condition was, of course, alleviated by the administration of carbohydrate and avoidance of excess dosage.

A year later, in 1923, Harris[53] suggested that there was a clinical possibility of spontaneous "hyperinsulinism," as he called it, as opposed to

the "hypoinsulinism" of diabetes. He had discussed this possibility with Banting, who, however, knew of no cases. Harris, convinced of the probability of his theory, watched for cases and, in his paper read in June, 1924, reported three with blood sugars below 70 mg. per 100 cc. whose symptoms improved by feeding. Although they did not suggest the term "hyperinsulinism" as such, Parker and Finley[115] antedate Harris by a publication in May, 1924, presenting the results obtained in ten cases of nervous phenomena treated with glucose. These were patients with low blood sugar and severe nervous manifestations, and the authors state that they were impressed with the similarity of these and cases of insulin hypoglycemia.

Four years after this suggestion came the first dramatic case of hyperinsulinism with a tumor of the pancreas. Wilder[163] and his colleagues reported this in 1927, a carcinoma of cells closely resembling island cells which had metastasized to liver, regional nodes and mesentery. The patient suffered from attacks of unconsciousness and had a blood sugar as low as 25 mg. Exploratory operation confirmed the anteoperative diagnosis, and autopsy was performed a month later. Extract of the liver nodule by Best's method for extracting insulin was said to act like insulin when injected into rabbits.

Following this, many cases were investigated for the disease entity hyperinsulinism, and the first surgical cure was effected by Roscoe Graham when he excised an island cell adenoma. This was published by Howland[66] and his co-workers in 1929. A year before this, Finney[43] had explored a case, and, finding no tumor, had resected 22.5 Gm. of the pancreas without alleviation of symptoms.

The clinical picture of the published cases which followed in rapid succession was extremely varied, but in general it may be said that hyperinsulinism is a chronic illness characterized by attacks at irregular intervals. If a careful history is obtained, these can almost always be related to the need of food, and many patients have learned by experience that an attack can be aborted by eating candy or sugar in other forms. In at least two cases frequent high carbohydrate feeding, either voluntary or prescribed, has resulted in extreme obesity. In Doctor Whipple's fourth case the patient had gained 100 pounds, which made the surgical approach difficult.

The symptoms are chiefly vasomotor and nervous. Wilder has grouped them under three main heads: those relating to disturbances of the vegetative nervous system; those of the central nervous system; and the less readily localizable psychic symptoms. The attacks vary all the way from mild feelings of fatigue, restlessness and apprehension, often with hunger, to maniacal seizures, convulsions, delirium and coma. In fact, they present, in varied combination, all the symptoms originally described by Banting in insulin shock. The most frequent diagnoses made before the hypoglycemia is discovered are epilepsy and alcoholism.

During the attacks the blood sugar is low. In cases examined pathologically where the lowest blood sugar is recorded the figures ranged from 4 to 58. It will be recalled that different methods of estimating the blood sugar give slightly different values and that different individuals vary in their tolerance of a low blood sugar. Also in the cases studied the same individual responds differently at different times. In general, children apparently can run a lower sugar without nervous effects than adults. In the intervals between attacks there are no symptoms, except occasionally persisting mental retardation or deterioration, and the blood sugar is often normal.

It is not our province here to detail the clinical findings. They may be found *in extenso* in three excellent reviews in English: Harris,[53] 1932, Wilder,[162] 1933, and Wauchope,[158] 1934, and in a monograph in French by Sigwald,[138] 1932. Also, as every one is aware, there are many causes of hypoglycemia which are not due to lesions of the pancreas, the most important and recognizable being disturbances of the adrenal, pituitary, thyroid and exhaustion of the glycogen reserve such as is found in diseases of the liver, and theoretically in muscular wasting, *i.e.*, the dystrophies. These conditions should be ruled out clinically before exploratory operation is justifiable.

There are also many instances of hypoglycemia in which none of the above conditions is found, and where the symptoms are mild enough so that operation does not seem justifiable. Many of these respond to diet, which can be so arranged that there is no excessive gain in weight. Hypoglycemia also occurs in the terminal stages of diabetes after the withdrawal of insulin. We have found 75 cases in the literature to date which were interpreted as hyperinsulinism or dysinsulinism (Table II).

TABLE II

Chronologic Data on Hyperinsulinism

Date	Author	Number of Cases	Date	Author	Number of Cases	
1924	Harris	3	1931	Gammon	1	
1925	Shih-Hao	1	1931	Moore	1	
1927	Stenström	1	1932	McGovern	1	
1928	Ravid	1	1932	Weil	1	
1928	Laroche	1	1932	Heyn	1	
1928	Pribram	3	1932	Briggs	3	
1929	Zubiran	1	1933	Rosenfeld	1	
1929	Hartmann	1	1933	Levi	1	
1930	Krause	1	1933	Sippe	25	
1930	Winans	3	1933	Love	1	
1930	Nielsen	3	1934	Jacobs	1	
1931	Waters	3	1934	Tedstrom	4	
1931	Valenzuela	3	1934	Rathery	1	
1931	Marsh	8				
		33			42	Total, 75

Also:

1924 Jonas: Hypoglycemia in a diabetic after discontinuance of insulin.
1927 Sjögren: Four diabetics with epileptiform seizures in hypoglycemic phases.
1928 Troisier: Hypoglycemia following traumatic hematoma of pancreas.
1930 Anderson: Tumor of adrenal with fatal hypoglycemia.
1931 Crawford: Primary carcinoma of liver with hypoglycemia.
1931 John: Hypoglycemia in diabetic after discontinuance of insulin.
1932 Stief: Medullary carcinoma of pancreas. No blood sugar recorded. Symptoms suggestive.
1932 Rabinovitch: Hypoglycemia with destruction of adrenal.

The following tables show all the cases which we have been able to find to date where the pancreas has been examined at operation or autopsy. They are listed chronologically, with the author's name, for many of them have been published several times. Table VII shows the cases of island cell tumors without recorded hypoglycemia.

Summarized, these figures are:

TABLE III.	Cases with tumor found at operation	21	(1 a carcinoma with metastases)
TABLE IV.	Cases with tumor found at autopsy.	10	
	Total cases with tumor...	31	
TABLE V.	Cases explored and no tumor found.	16	Normal pancreas..... 10
			Pancreatitis..... 3
			Hypoplasia (?)..... 1
			Hypertrophy..... 1
			Tumor found at autopsy.... 1
			16
TABLE VI.	Cases with autopsy, no tumor found	3	All showed hypertrophy
	Total cases without tumor	18	
TABLE VII.	Cases with tumor without recorded hypoglycemia.....	31	
	Total cases with tumor...	62	

From the surgical standpoint there are several extremely interesting features. There has been only one operative death in the group. This does not mean that the operation is without technical difficulties, but that the operators were men experienced in the surgery of the pancreas and able to obtain adequate exposure without undue trauma. The exposure is of great importance, since the tumors are usually small.

All of the cases with tumors recognized and excised have been relieved of symptoms. Of the cases with no tumor, resection has given complete relief of symptoms in five out of 15. These are the last five cases reported and in these much more of the gland was resected than had been previously attempted. The follow up on these cases is necessarily short.

Pancreatic fistula as a postoperative complication has been reported only four times.

Insulin has been recovered three times from the tumors, or rather an extract of the tumor has acted like insulin on test animals.

In general, it may be said that hypoglycemia may occur without demonstrable lesion in the pancreas, and that tumors can occur without hypoglycemia (30 cases), although this phase was not very thoroughly investigated in the early cases reported. In this connection, through the courtesy of Doctor Pappenheimer of the Department of Pathology, we are able to report that in 4,010 consecutive autopsies five island cell adenomata have been found, roughly one in a thousand cases. In four it was an incidental finding. The fifth case has been published by Wolf.[165]

The tumors are in general small, the most common measurement being 1.5 cm. in greatest diameter. Only two of the surgical cases of benign tumor were large, one 9 by 9 by 11 cm., weighing 500 Gm., and the other a trilobed tumor, the largest lobe measuring 3 by 1.5 by 1 cm. In the cases without recorded symptoms of hypoglycemia the tumors are almost all small with two striking exceptions.

The most common site of the tumors is near or in the tail, where, it will be recalled, the islands are most numerous. They may be multiple, an important fact for the surgeon to bear in mind. The tumors are grossly encapsulated, and the more usual color in the living patient is reddish, in contrast to the yellower surrounding pancreatic tissue. A few of the tumors which showed fibrosis, and sometimes even calcification, were hard, but the consistency is not usually very different from that of the surrounding tissue. This makes it difficult to find the tumors which are deep in the substance of the gland. Most of the surgical cases fortunately have been close to the capsule of the organ.

Microscopically, the tumors are not all encapsulated and in some of them the diagnosis of carcinoma has been suggested on the basis of microscopic invasion, variation in morphology of the cells, and tumor cells in the vessels. Only three of the 62 cases of island cell tumor of the pancreas have shown metastases (Wilder,[163] Hamdi[51] and Judd[72]). Possibly these will appear later in some of the cases of excision where the microscopic appearance of the tumor has suggested malignancy. It is difficult to draw the line on the one hand between the highly differentiated tumors and simple hypertrophy, and on the other between the benign and malignant forms of the less differentiated tumors. Our own series of pathologic findings illustrates this variability, and a longer follow up on all these cases may show whether a diagnosis of carcinoma is justified, though, of course, metastasis may have been prevented in some instances by early removal of the tumor.

All of the tumors show cells which resemble somewhat the cells of normal islands, but there are many deviations. In a few, beta cells have been recognized in large numbers by the specific staining reactions. Many of the tumors were not so studied. The largest single series reported with careful examination is that of O'Leary and Womack[113] (five tumors). It is interesting that these observers, both unusually qualified by previous experience for the study, conclude that "the majority cell type of each (tumor) was closely allied to the beta cells of the normal islets of Langerhans, but pos-

TABLE III

Hypoglycemia with Island Cell Tumor. Cases with Operation

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Operation	Site Tumor	Size Tumor	Insulin Recov. Spec.	Pathology	Result	Fistula Postop.	Autopsy
Wilder, R. M. Allan, F. N. Power, M. H. Robertson, H. E.	J. A. M. A., 1927, 89:348–355	40	M.	20 mos.	Mental. Loss consciousness	25	Exploratory	Tail	Whole tail	Yes. From liver metas.	Carcinoma with metas. to liver	Died 1 mo. postop.	0	Carcinoma of pancreas, metas. to liver
Mathias	Med. Klin., 1928, 24:1814	?	?	?	?	Low	Excision of pancreatic cyst	In wall of cyst	?	0	Multiple adenomatous islands in wall of cyst	Mild glycosuria after operation	?	—
Howland, G. Campbell, W. R. Maltby, E. J. Robinson, W. L.	J. A. M. A., 1929, 93:674–679	52	F.	7 yrs.	Coma	40	Excision of adenoma (Roscoe Graham)	Middle	1.5 cm.	0	No capsule microscopically. Parenchymal glands in center	14 wks. clinically cured	*Note:* Erratic response to carbohydrates (dysinsulinism ?)	
Carr, A. D. Parker, R. Grove, E. Fisher, A. O. Larrimore, J. W.	J. A. M. A., 1931, 96:1363–1367	19	M.	22 mos.	Confusion. Stupor	44	Excision	Mid portion	1 x 2 cm.	0	Encapsulated beta cell adenoma	Immediate result: good	0	—
Womack, N. A. Gnagi, W. B. Graham, E. A.	J. A. M. A., 1931, 97:831	44	M.	3 mos.	Convulsions	50	Excision	Junction body and tail	1 x 2 cm.	0	Not encapsulated Adenoma or carcinoma	No attacks 2 yrs.	+	—
Bast, T. H. Schmidt, E. R. Sevringhaus, E. L.	Acta chir. Scandinav., 1932, 71:82	44	M.	Not stated	Coma	27	Excision	Tail	2.5 cm.	0	Not encapsulated	8 wks. improved	—	—
Tomkies, J. S.	Texas State Jour. Med., 1932, 28:523	30	M.	3 yrs.	Unconsciousness	41	Resection part of body and part of tail	Body	Trilobed. Largest lobe: 3 x 1.5 x cm.	0	Encapsulated	14 mos. symptom free	0	—
Derick, C. L. Newton, F. C. Schulz, R. Z. Bowie, M. A. Pokorny, N. A.	New Eng. Jour. Med., 1933, 208:293	56	F.	6 yrs.	Coma	38	Tail resected	Tail	1.6 x 1.2 cm.	+	Encapsulated	Symptom free 20 mos.	0	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	45	M.	4 yrs.	Coma	30	Excision	Body	3 cm.	0	Carcinoma of islet cells. Not encapsulated	Symptom free 22 mos.	+ 9 mos.	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	32	M.	1 yr.	Mental confusion	40	Excision	(1) Junction body and tail	1.5 cm.	0	Carcinoma	Symptom free 23 mos.	0	—
								(2) Body	2 cm.		Not encapsulated	Mild diabetes		

Graham, E. A. Womack, N. A.	Surg., Gynec. and Obst., 1933, 56:728–742	22	M.	5 yrs.	Petit mal confusion	25	(1) Nodule excised (2) 4 cm. tail excised	Tail	(1) 1 x 0.8 cm. (2) 2 x 1.4 x 1.2 cm.	+	(1) Nodule, adenoma degenerated (2) Nodule, adenoma partially encapsulated	No attacks. Permanent central nervous system damage		—
Graham, E. A. (not published)	1933, quoted by O'Leary and Womack	52	M.	2 yrs.	?	?	Excision	?	9 x 9 x 11 cm. Wgt. 500 Gm.	?	Yellow-gray. Carcinoma (?). Cells in vessels. Encapsulated	Improved	?	—
Aitken and Fischer (not published)	1933, quoted by O'Leary and Womack	44	F.	4 yrs.	?	?	Excision	?	1.5 x 0.8 cm.	?	Yellow-gray. Adenoma. Partially encapsulated	Improved	?	—
Ross, L. I. Tomasch, J. M.	Arch. Surg., 1934, 28:224–231	33	M.	1 mo.	Coma	23	Excision	Middle	1.5 x 2 cm.	o	Adenoma	Symptom free 10 mos.	—	—
Judd, E. S. Faust, L. S. Dixon, R. K.	West. Jour. Surg., 1934, 42:555–557	18	F.	3½ mos.	Coma	45	Biopsy liver Expl.	"Tumor pancreas"	?	o	Multiple metastases in liver. Islet cell carcinoma	Died 4 wks. postop. with hypoglycemia	o	o
Whipple, A. O. Case I. Neurol. Inst. Pres. Hosp. No. 380424	In Press*	33	F.	1 yr.	Unconsciousness	30	Excision	Junction body and tail	1.5 x 1 x 1 cm.	o	Adenoma	Symptom free 15 mos.	o	—
Whipple, A. O. Case II. Neurol. Inst. Pres. Hosp. No. 421465	In Press*	48	F.	9 mos.	Confusion	34	Excision	Junction body and head	1.3 x 1.2 x 1 cm.	o	Adenoma	Symptom free 9 mos.	o	—
Whipple, A. O. Case IV. Neurol. Inst. Pres. Hosp. No. 428308	In Press*	38	M.	12 yrs.	Confusion	30	Excision 2 tumors	(A) Lower border body. (B) Head	(A) 1.5 cm. (B) 1.0 cm.	o o	Adenoma Adenoma	Symptom free 7 mos.	+ 3 mos.	—
Whipple, A. O. Case III. Neurol. Inst. Pres. Hosp. No. 306695	In Press*	28	M.	3 yrs.	Mania. Delirium	38	(1) Excision (2) Excision	(1) Junction body and head (2) Tail	(1) 1.4 cm. (2) 2 x 1.5 cm.	o	Adenoma	Symptom free 7 mos.	o	—
Whipple, A. O. Case V. Neurol. Inst. Pres. Hosp. No. 434384	Not published	28	F.	6 yrs.	Unconsciousness	30	Resection tail and part of body	Body 2 nodules	(a) 1.2 cm. (b) .3 cm.	o	Adenoma	Symptom free 4 mos.	o	—
Whipple, A. O. Case VI. Neurol. Inst. Pres. Hosp. No. 350794	Not published	45	F.	4 yrs.	Unconsciousness	28	Excision	Junction body and tail	2 x 1.6 x 1.8 cm.	o	Adenoma	Symptom free 2 mos.	o	

* Proc. Inter-State Post-Graduate Med. Assn. of North America.

TABLE IV

Hypoglycemia with Island Cell Tumor. Cases with Autopsy

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Site Tumor	Size Tumor	Insulin Recov. Spec.	Pathology	Autopsy
Thalhimer, W. Murphy, F. D.	J. A. M. A., 1928, 91:89–91	57	F.	2½ yrs.	Unconsciousness	33	Junction of tail and body	1 x 1.5 cm.	0	Microscopic invasion of capsule	No metastases
McClenahan, W. U. Norris, G. W.	Am. Jour. Med. Sci., 1929, 177:93–97	41	M.	45 mos.	Loss of memory; unconsciousness	20	Junction middle and distal third	1.5 x .7 x .6 cm.	0	Adenoma not microscopically encapsulated	No metastases
Smith, M. G. Seibel, M. G.	Am. Jour. Path., 1931, 7:723–739	40	M.	7 yrs.	Coma	58	Center of head	1 cm.	0	Mostly encapsulated	No metastases
Terbrüggen, A. (Frank, H.)	Beitr. z. path. Anat. u. z. allg. Path., 1931, 88:37–50	30	F.	1 yr.	Coma	23	Middle and tail	2 x 1.5, 1 and 1.5 cm. and smaller	0	Multiple adenomata	No metastases
Büchner, F. Bielschowsky, F.	Klin. Wchnschr., 1932, 11:1494–1496	57	M.	? Diabetes. Not stated	Coma	31	Distal one-third	1 x 1.1 x .7 cm.	0	Encapsulated	Cirrhosis of pancreas. No metastases
Gibbs, C. B. F.	N. Y. State Jour. Med., 1932, 33:638	34	F.	9 mos.	Coma	17	Tail	1.3 x .7 x 1.0 cm.	0	Encapsulated grossly. No microscopic examination reported	Right adrenal hemorrhagic cyst
Barnard, W. G.	Jour. Path. and Bact., 1932, 35:929–932	40	F.	3 mos.	Coma	20	Head	1.2 cm.	0	Not encapsulated	No metastases
Cairns, R. M. Tanner, S. E.	Brit. Med. Jour., 1933, 1:8	52	F.	1 yr.	Unconsciousness	41	Tail	2 cm.	0	Gray. Adenoma. Encapsulated	No metastases
Wolf, A. Hare, C. C. Riggs, H. W.	Bull. of Neurol. Institute, 1933, 3:232	10	M.	16 mos.	Convulsions	54	Middle. Tail. Head	1 cm. .3 cm. .3 cm.	0	Encapsulated	No metastases
Rienhoff, Wm. F., Jr. Lewis, D.	Bull. Johns Hopkins Hosp., 1934, 54: 386–429	39	M.	18 mos.	Unconsciousness	4	Head	2.2 x 1.2 x .9 cm.	0	Circumscribed	No metastases. See chart

TABLE V

Hypoglycemia. No Tumor Found at Operation

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Operation	Pathology	Result	Fistula Postop.
Finney, J. M. T. Finney, J. M. T., Jr.	Trans. Am. Surg. Assn., 1928, 46:268	53	F.	4 yrs.	Spells unconsciousness	30	Resection 22.05 Gm.	Normal pancreas	Attacks continued	o
Allan, F. N. Boeck, W. C. Judd, E. S.	J. A. M. A., 1930, 94:1116	52	M.	2 yrs.	Stupor	40	14 Gm. excised; tail and part of body	Normal	14 mos. no improvement	o
Allan, F. N. Boeck, W. C. Judd, E. S.	J. A. M. A., 1930, 94:1116	47	M.	4 yrs.	Convulsions. Mania	40	8 Gm. excised	Normal	4 yrs. no improvement	+
Harris, S. (Taylor)	J. A. M. A., 1933, 100:321	20	M.	2 yrs.	Narcolepsy	50	½ body and tail excised	Normal	2 yrs.	o
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	50	M.	14 mos.	Coma	40	(1) 8 Gm. tail excised (2) Pancreas clamped	Normal	No permanent improvement	—
Judd, E. S. Allan, F. N. Rynearson, E. H.	J. A. M. A., 1933, 101:99	42	M.	1 yr.	Coma	20	Capsule stripped	Pancreas chronic inflammation ½ usual size	Improving but with diet	—
Holman, E. (1928) Railsback, O. C. Judd, E. S. (1932)	Surg., Gynec., and Obst., 1933, 56:591–600	31	M.	2 yrs.	Convulsions Coma	32	(1) Resection 1928 (2) Excision nodule 1932	Interstitial pancreatitis	Unimproved	—
Evans, J. A. McDonough, W.	Jour. Iowa Med. Soc., 1933, 23:454	41	F.	1 yr.	Spells	?	Resection	Normal pancreas	Unimproved	
Winans, H. M.	Am. Jour. Med. Sci., 1933, 185:500	30	F.	15 yrs.	Convulsions	35	Biopsy	Normal. Slight hypoplasia?	No relief	
Ziskind, E. (Bayley)	Arch. Int. Med., 1933, 52:76	19	M.	18 mos.	Coma	40	Resection 7.2 Gm.	Normal pancreas	Unimproved	o
Graham, E. A. Hartmann, A. F.	Surg., Gynec., and Obst., 1934, 59:474	1	M.	9 mos.	Convulsions	6 ("true" sugar)	80–90% resected	Normal pancreas	Symptom free 9 mos.	o
Harris, Seale (Drennan)	Southern Surgeon, 1934, 3:109	32	F.	?	Fainting	60	Excision ½ body and tail	Normal pancreas	Relief of symptoms 4 mos.	o
Harris, Seale (Drennan)	Southern Surgeon, 1934, 3:109	27	M.	4 mos. (8 yrs.)	Convulsions (Petit mal)	65	Excision ½ body and tail	Pancreatitis	Convalescent	o
Simon	Southern Surgeon, 1934, 3:109	26	M.	3½ mos.	Unconsciousness	51	Resection 60 Gm.	Hypertrophy islets	Improved 2 mos. +	o
Thomason, G.	Personal communication, 1934. Western Surg. Assn., Dec. 8, 1934.	?	M.	?	?	?	Subtotal resection. Tail and body	No adenoma	Improved (no. mos. ?)	o
Rienhoff, Wm. F., Jr. Lewis, D.	Bull. Johns Hopkins Hosp., 1934, 54:386–429	39	M.	18 mos.	Unconsciousness	4	Resection tail and half body	Normal pancreas	Died shock first day postop. See TABLE II	—
Boone, J. A.	New England Jour. Med., 1934, 211:49–53	11	F.	10 mos.	Unconsciousness	37	Exploratory. Biopsy	Normal pancreas	To be followed	o

TABLE VI

Hypoglycemia. No Tumor Found at Autopsy

Author	Publication Date	Age	Sex	Duration Symptoms	Type Symptoms	Min. Bld. Sugar	Pathology	Other Autopsy Findings
Massa, M.	Gior. di clin. med., 1929, 10:679	67	M.	2 mos.	Referable to carcinoma	58	Hypertrophy of islands	Adenocarcinoma of pancreas with obstruction of ducts and metastases
Phillips, A. W. Mosenthal and MacBrayer (not published)	J. A. M. A., 1931, 96:1195 1933 Quoted by Wilder	56 39	M. M.	11 mos. 3 yrs.	Coma (nephritis) Vertigo	25 50	Hypertrophy of islands Hypertrophy of islands	

TABLE VII

Tumors with No Recorded Hypoglycemia
(Not Interpreted as Simple Hypertrophy)

Date	Author	Age	Sex	Diabetes	Autopsy or Operative Findings	Site of Tumor	Size of Tumor in Mm.	Encapsulation
1902	Nicholls	?	?	?	?	?	3.0 x 2.5 Mm.	+
1905	Reitman	62	M.	+	Chronic interstitial pancreatitis. Cardiovascular disease	?	?	?
1906	Herxheimer	67	F.	+	Diabetes. Chronic cardiac vascular disease	?	2 adenomas. Larger 4 x 2 Mm.	+
1907	Helmholz	65	M.	?	Chronic cardiac vascular lisease	?	5 x 5 x 3 Mm.	+
1908	Morse	44	F.	?	Peritonitis	Splenic end	5 Mm.	+
1908	Morse	46	M.	?	Cerebral hemorrhage. Arteriosclerosis. Chronic nephritis	?	3 Mm.	+
1909	Cecil	75	M.	+	Diabetes. Pneumonia	?	1.8 x 1.6 Mm.	?
1910	Weichselbaum	?	?	—	?	?	1.5 Mm.	?
1911	Cecil	63	M.	—	Carcinoma of colon	?	4 x 3.5 Mm.	?
1911	Heiberg	64	F.	+	Diabetic coma	?	6 x 5 Mm.	+
1911	Alezais and Peyron	?	?	?	?	?	"Petit pois"	o
1912	Rollett	25	F.	—	Pulmonary tuberculosis and tuberculous peritonitis	?	11 Mm.	?
1913	Lecomte	42	F.	—	Tuberculosis of cerebellum	Junction of head and body	100 x 70 x 40 Mm.	+
1914	Koch	22	F.	o	Multiple sclerosis. Bronchopneumonia	Middle	14 Mm.	+
1922	Priesel	63	F.	?	Arteriosclerosis. Myocarditis and pneumonia	Lower border	12 x 10 x 9 Mm.	+
1922	Priesel	51	M.	?	Arteriosclerosis. Encephalomalacia. Pneumonia	Head	9 x 10 Mm.	+
1922	Priesel	60	M.	?	Arteriosclerosis	?	35 x 25 Mm.	+
1924	Schneider	84	M.	o	Myocarditis. Bronchopneumonia. Sclerosis of kidneys	Middle	"Pruneau"	+
1924	Schneider	60	F.	o	Tuberculosis	Middle	50 x 45 x 30 Mm.	+
1925	Lang	34	F.	o	Bronchopneumonia—postoperative	Throughout	up to 5 Mm.	+
1926	Warren	53	F.	o	Carcinoma of ovaries	?	1.7 x 1.7 x 1.4 Mm.	+
1926	Warren	63	M.	o	Myocarditis	?	1.3 x 1.1 Mm.	+
1926	Warren	49	F.	o	Pernicious anemia	?	1.2 x 1.2 Mm.	+
1926	Warren	48	F.	o	Chronic nephritis	Junction of head and body	9.0 x 6.5 x 6.0 Mm.	+
1928	Natali	60		o	Carcinoma of stomach with metastases	Tail	14 x 15 Mm.	+
1929	Lloyd	27	F.	o	Hypophyseal tumor. Enlarged parathyroids	5 cm. middle and outer 1/3	Multiple — largest 10 x 7 x 6 Mm.	+
1931	Smith	?	M.	o	Carcinoma of liver	Body	10 Mm.	+
1931	Smith	50	M.	o	Periods of loss of memory. Died following operation for gallstones	?	6 Mm.	+
1932	Smith	48	F.	+	Lobar pneumonia. Thrombosis of iliac veins. Pulmonary embolus	Body	10 Mm.	+
	Hamdi	52	M.	?	Tumor of tail with metastasis in liver. (No clinical history.)	Tail	2 x 2.5 Mm.	?
1933	Cottalorda	32	F.	?	Large pedunculated bilobed tumor attached to tail. Excision	Tail	130 x 80 Mm.	+

sessed definite tumor characteristics," and that "the staining reactions of the specific granules in the majority of tumor cells of each deviated sufficiently from those of the beta cells of normal human islets to lend support to the hypothesis of dysinsulinism."

Our own series consists of eight tumors removed by Doctor Whipple from six patients with symptoms of hypoglycemia (TABLE III). All of the patients were relieved of their symptoms postoperatively. Cases I, II, V and VI had single tumors. Case III had two tumors removed at the same operation; Case IV had one tumor removed which was of the island cell type with some degeneration. Because of persisting symptoms he was operated upon again a month later and a second similar tumor was found and excised. His symptoms were relieved after the second operation.

For comparison with the tumors, Fig. 1 shows a normal human island. An island is a typical endocrine structure of columns of cuboidal and pyramidal cells interwoven with blood capillaries to form an intricate network of three dimensions. The island cells are ranged along the capillaries, and where a capillary has been cut across the island cells appear to form a rosette around it. The majority of the cells in normal islands of average size are beta cells. We have been unable to identify a third granular cell so far in normal guinea-pig or human pancreas. The larger capillaries are lined by endothelium outside of which there is a thin layer of fibrous connective tissue. In many of the smaller blood channels no endothelial lining is seen. Some of them appear to consist of extremely thin tubes of collagen together with a fenestration of reticulin. Around the island there is a delicate capsule of fibrous connective tissue richly provided with blood vessels. In normal human islands the fibrous tissue is scanty. In diabetes it is around the vessels that the hyaline change first described by Opie is seen. In his own words:[114] "The term hyaline degeneration is wholly descriptive and is applied to the ill-defined group of degenerative processes of which the common character is the formation of homogeneous or hyaline material. In the island of Langerhans hyaline occurs as conspicuous masses in contact with capillaries, the endothelium of which is well preserved. The islet cells are partly or completely destroyed and replaced."

Our first tumor (Fig. 2) measured 1.5 by 1 by 1 cm. and was removed from the junction of the body and the tail where it lay just beneath the capsule of the pancreas. A small rim of pancreatic tissue was removed with it. The tumor in the fresh state was pinkish-red, more vascular than the surrounding gland. Microscopically, it is completely encapsulated. There is no evidence of compression of the surrounding pancreatic tissue, nor is any striking hyperplasia of island tissue seen in the pancreas. Only a rare mitotic figure is seen in the tumor cells and no tumor cells are found in vessels. In architecture this tumor very closely resembles a normal island. There is the same grouping of cuboidal and pyramidal cells in columns along the capillaries or in rosettes around a capillary. The endothelial lining of the vessels is sometimes distinct, sometimes not. Where

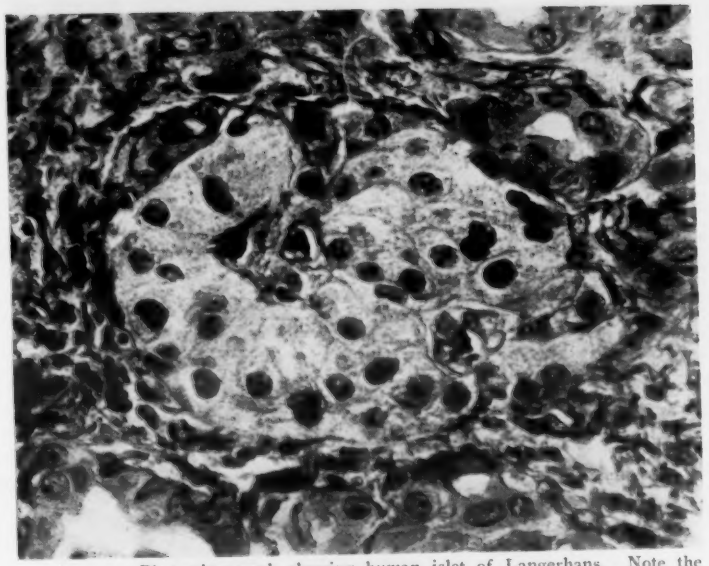

FIG. 1.—Photomicrograph showing human islet of Langerhans. Note the granular cells and their relation to the capillaries. The surrounding pancreas is not entirely normal but shows some fibrosis.

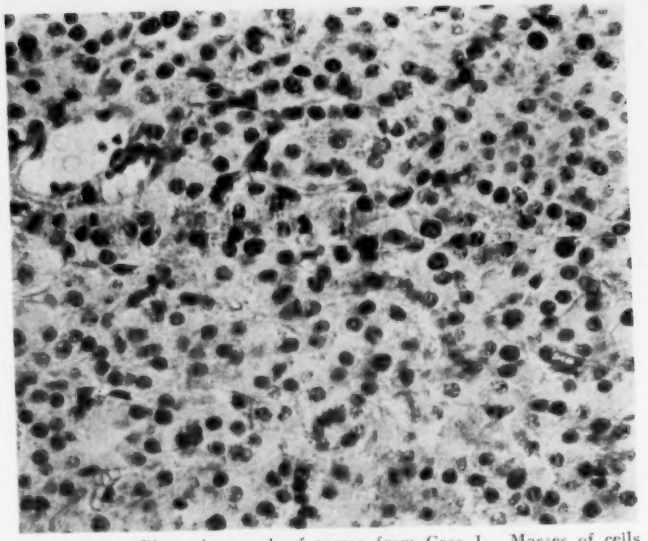

FIG. 2.—Photomicrograph of tumor from Case I. Masses of cells are seen in intimate relationship with capillaries. This closely resembles a normal islet.

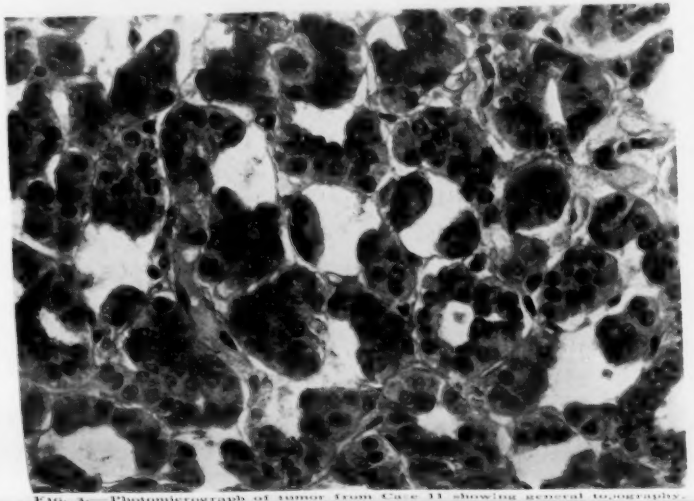

FIG. 3.—Photomicrograph of tumor from Case II showing general topography

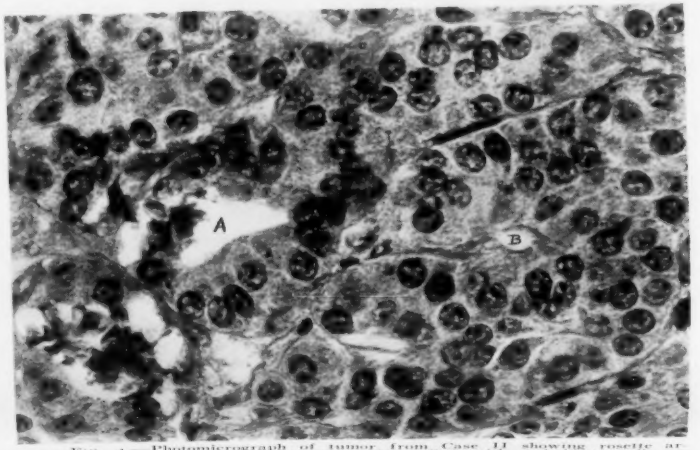

FIG. 4.—Photomicrograph of tumor from Case II showing rosette ar[rangement] of cells around spaces. (A) Filled with red blood cells a[nd]

it is not recognized, thin walled tubes of collagen are seen together with a fine network of reticulin. In one area near the capsule there is a disseminated fibrosis limited to the capillaries. Around many of these there is a thick wall of fibrous connective tissue. The fibrosis often takes the form of a solid block of collagen situated on one side of the capillary. The distribution of the fibrous connective tissue, both collagen and reticulin, is shown best by Masson's trichrome, Van Gieson and Laidlaw's silver connective tissue stain.

Our second tumor (Figs. 3 and 4) measured 1.3 by 1.2 by 1 cm. It was removed from the junction of the body and head. Grossly it was encapsulated and had attached to it a small rim of pancreatic tissue. It was dark bluish-red and uniform. Microscopically, this tumor is also encapsulated, but the capsule was exceedingly delicate. Only a rare mitotic figure is seen, there is no invasion and no tumor cells are found in vessels. There is more distinct rosette formation than in the first. Sometimes the rosettes are distinctly formed about endothelial lined capillaries, sometimes about small tubes of collagen and sometimes there are lumina lined directly by tumor cells. These appear as ductlike structures. Whether they are to be interpreted as adult ducts from the original pancreatic tissue, or new formed tumor ducts, is difficult to say. The low columnar cells lining them have their polarity well preserved and show between their distal extremities the "Schlussleisten" characteristic of the adult form. But they occur in the center of the tumor and may well represent new growth. The point is rather an academic one, since the origin of island cells from duct epithelium has been demonstrated. We have regarded this tumor as a somewhat more embryonal form than Case I. It shows, however, a considerable degree of fibrosis and some degeneration closely related to the "hyaline" type already discussed.

Our third and fourth tumors (Figs. 5 and 6) removed from Case IV at the same operation show what we have interpreted as a still more embryonal, less differentiated type. These tumors measured 1.5 cm. and 1 cm. in greatest diameter respectively. Tumor A was removed from the body and tumor B from the head of the pancreas. They were both encapsulated grossly. Both were grayish-red. Microscopically, the tumors are not completely encapsulated, but the tumor cells show in sharp contrast to the acinar cells because of the characteristic mitochondria which are very striking in the latter. This tumor likewise shows only a rare mitotic figure, no evidence of invasion and no tumor cells in blood vessels. The cells are cylindrical or polyhedral cells arranged in cords giving the appearance of winding ribbons. Sometimes the ribbon appears to be wound around a capillary so as to form a rosette. Occasionally ducts are seen as in Case II. Tumor A differs from tumor B in this case by showing a much greater degree of degeneration and fibrosis. The same pale blue staining material (Masson stain), which does not show reticulin fibers in the special stains, and which is paler than the collagen fibers, is found in

masses about the capillaries, sometimes with distinct shadows of cell outlines, and sometimes as blue masses in otherwise well preserved cells. In all of our cases this material does not appear strictly hyaline, in that it is not homogeneous, but somewhat granular. It does not react for mucin with the mucicarmine stain nor is it amyloid.

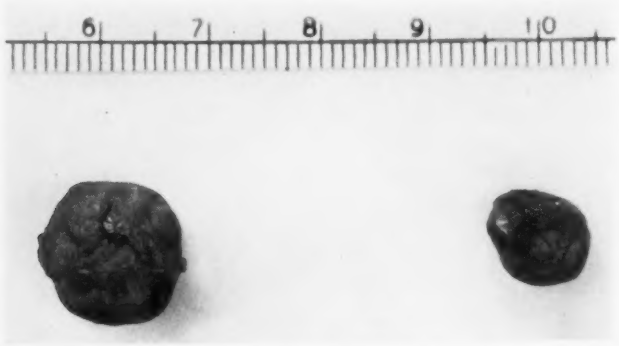

FIG. 5.—Gross photograph of two tumors removed from Case IV showing size against a centimeter scale.

Our fifth and sixth tumors (Figs. 7 and 8) removed from Case III one month apart came from the junction of the body and head and from deep in the substance of the tail. The first measured 1.4 cm. in greatest diameter, the second 2 by 1.5 cm. Both appeared partially encapsulated and

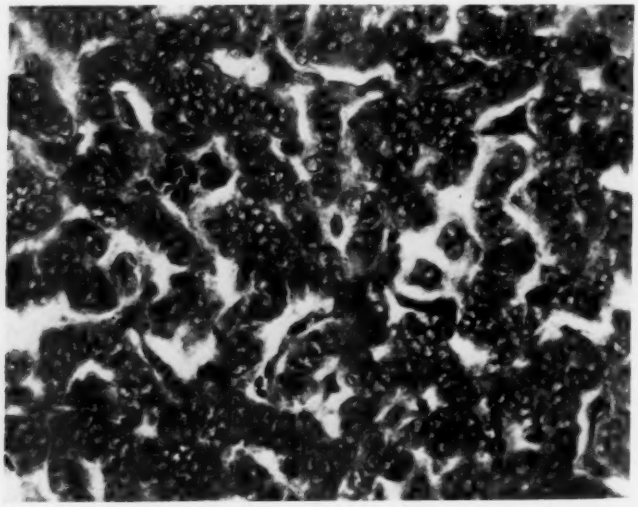

FIG. 6.—Photomicrograph of a section from the smaller of the two tumors from Case IV, showing ribbon-like arrangement of cells.

reddish. Microscopically, these tumors are not sharply demarcated from the surrounding pancreatic tissue. Acinar cells, distinguishable by their mitochondrial striations and their zymogen granules, are found among the tumor cells in the periphery of the tumor. Whether this indicates in-

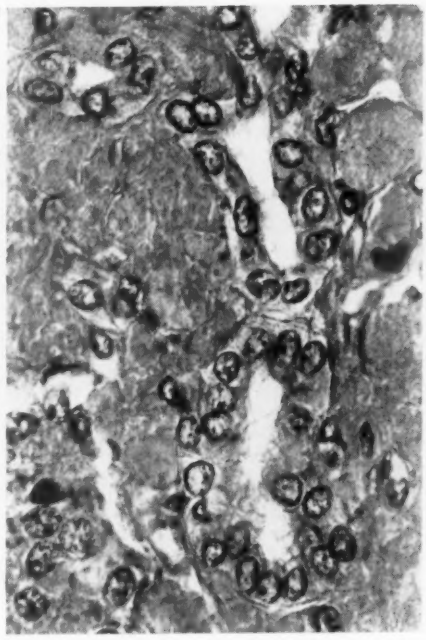

Fig. 7.—Photomicrograph of tumor I from Case III showing duct formation.

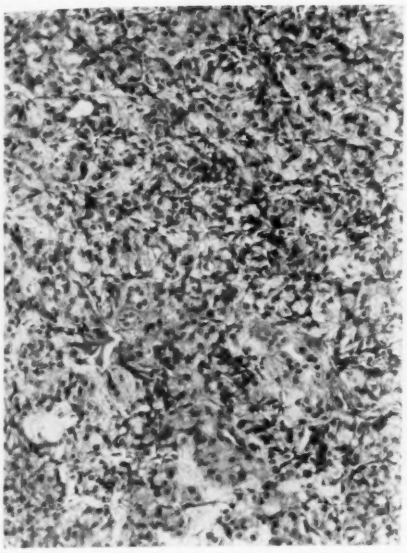

Fig. 9.—Photomicrograph of tumor from Case V showing ducts.

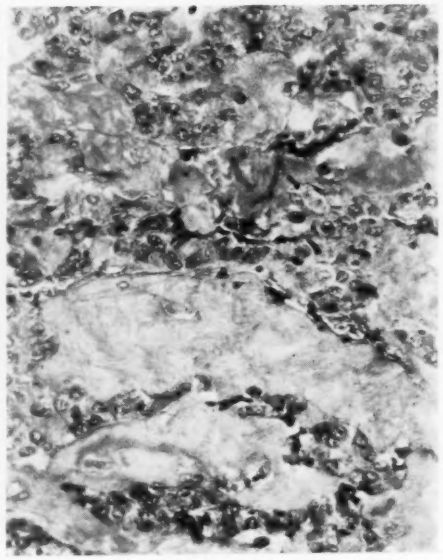

Fig. 8.—Photomicrograph of tumor II from Case III showing degeneration.

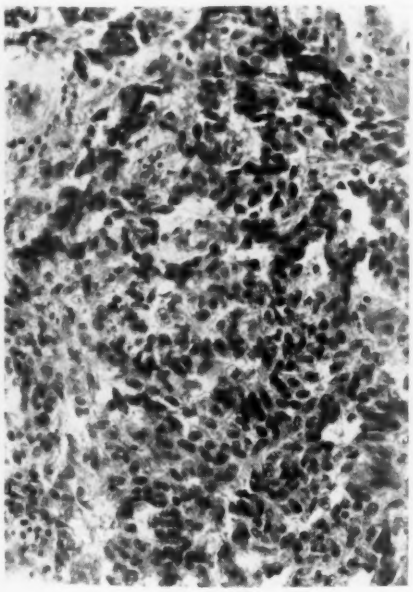

Fig. 10.—Photomicrograph of tumor from Case VI.

vasiveness on the part of the tumor cells is difficult to say. Only a rare mitosis is observed and no cells are found in blood vessels. The striking feature of both these tumors is the degeneration. Broad bands of pale blue-staining material (Masson stain) are found everywhere in the section so that the predominant arrangement of the tumor cells is hard to distinguish. Some ribbon arrangement is seen, some rosette formation around capillaries, and some tubules or ducts.

Our seventh tumor (Fig. 9) from Case V came from the body of the pancreas and consisted of a circumscribed mass 1.2 cm. in greatest diameter. A third of this was calcified. Adjacent to this portion there was a second smaller completely encapsulated mass 4 by 3 by 3 Mm. Both of these tumors closely resemble the tumors from Case IV in the extensive degeneration and fibrosis. The tumor cells are arranged in strands with occasional rosette formation around a capillary. More ducts are present in this tumor than in any other of our series. No mitotic figures are observed.

Our eighth tumor (Fig. 10) from Case VI was the largest of our series, measuring 2 x 1.6 by 1.8 cm., and came from the junction of the body and tail. It was nodular, and apparently completely encapsulated. On section portions of the mass were firm and white, while other areas were softer and yellower. Microscopically, this tumor shows extensive areas of degeneration and fibrosis, and only an incomplete capsule. The relationship of cells to the capillaries is not as striking as in the previous cases, and there are many more ducts in the tumor than in any of the others. No mitoses are seen. Dr. Margaret Murray will report on the cultivation *in vitro* of the tumor cells of these last two cases.

With the specific stains for alpha and beta granules neither the tumor cells nor the island cells of the surrounding pancreas uniformly show the granules definitely colored. In the two tumors from Case III, a few cells are scattered through the section with granules staining like beta cells. In the tumor from the last case with the acid fuchsin-methyl green method of Bensley the majority of the tumor cells show granules similar to those in the majority of cells in the normal islands of the adjacent pancreas. Further work on these specific stains is in progress, and we are not, therefore, in a position to make any positive statement about the granular properties of the tumor cells at this time. (See note p. 1327.)

We have classified these eight tumors as adenomata, for the present at least, and only in the fifth, sixth, and eighth have we seen any evidence of what might be considered an infiltrating tendency. Marked variation in the size and shape of cells, mitotic figures in any appreciable number and blood vessel invasion are nowhere present. In each case the tumor appears to have been completely excised. In all of the tumors the morphology is that of an endocrine gland. That they were functionally active is obvious from the fact that the patients no longer suffer from hypoglycemia after their removal. It is unfortunate that we are unable to report any successful attempt to extract insulin from the tumors.

Case Reports

Case I.—F. K. (Presbyterian Unit No. 389424. Neurological Institute No. 1), a 33-year-old Polish woman, married, complaining of spells of unconsciousness for one year.

Family and Past History.—Entirely irrelevant.

Present Illness.—In January, 1933, without prodromata of any sort she was suddenly seized with a "spell." She remembers nothing concerning this and when the "spell" was over she felt as well as ever. A few days later she developed headache which recurred from time to time with no known cause. The "spells" continued, and August 8, 1933, she was admitted to the Neurological Institute in coma. Her husband said that her "spells" were associated with dizziness and vomiting. There was a definite histronic spasm prior to this attack, and in others a peculiar type of giggling and grimacing. No visual disturbance or motor disability other than that of speech.

Under the impression that the patient had some sort of encephalitis she was treated with forced spinal drainage with intravenous solution of glucose. The blood sugar two days after admission with this treatment showed 145 mg. per 100 cc. Her next sugar determination was not until September 12, at which time a value of 65 mg. was found. She was then intensively studied. Her first sugar tolerance test was performed November 9, at which time her fasting blood sugar was 30.3 mg. per 100 cc.

The patient continued to have periodic seizures. Blood sugar determination at these times invariably showed a low level. She was also tested out by calculated diets, by insulin, and by adrenalin, with no significant change in the sugar level. She was then transferred January 6, 1934, to the Surgical Service at the Presbyterian Hospital. Further blood studies were done before operation.

Physical Examination.—Well-developed, well-nourished, slightly obese. Temperature, 98°; respirations, 20; pulse, 84; blood pressure, 120/80. General physical examination, essentially negative. Reflexes, normal.

Operation.—January 11, 1934, under spinal anesthesia. A transverse incision was made through both recti. A tumor about 1 cm. in diameter was removed from the junction of the body and tail of the pancreas.

Postoperative Course.—The wound healed by primary union. No pancreatic fistula. The sutures were removed on the seventh day. The patient was allowed up on the fourteenth day, and discharged from the hospital on the twentieth day. She had no seizures following operation.

Follow Up.—Fifteen months postoperative. Patient symptom free. No complaints. No hernia. Working at full capacity. Scar firm.

Case II.—S. B. (Presbyterian Unit No. 421465. Neurological Institute No. 2), a Jewish housewife, 48 years of age, was admitted to the Neurological Institute April 4, 1934.

Family and Past History, negative.

Present Illness.—Since August, 1933, about nine months ago, patient has become unusually irritable and shows episodes of agitation without adequate cause. The attacks usually last about 20 minutes and are preceded by colored scotomata in the form of rings. Mental confusion is also present and the patient does not remember the episodes clearly. They are followed by somnolence. The attacks usually come around 11:30 A. M., no breakfast being eaten as a rule, because of a late supper at night. The family states that an attack can be prevented occasionally by giving food. The attacks have continued and become longer as well as more frequent, so that for the past six to seven months they have occurred almost daily. Occasionally they are accompanied by purposeless, thrashing movements of the extremities, body and head, as well as negativism, muttering, facial flushing, and profuse diaphoresis.

Physical Examination.—Patient is a rather obese, white woman, very irritable and uncoöperative. Temperature, 99.4°; pulse, 75; blood pressure, 160/100. The general examination is essentially negative otherwise.

Laboratory Findings.—Urine negative. Hemoglobin, 87 per cent; red blood cells, 4,800,000; white blood cells, 9,000; polymorphonuclears, 80 per cent. Wassermann, negative. Blood urea, 10.9. Blood sugar, 43 mg. per 100 cc. Skull roentgen ray negative. Gastro-intestinal series, negative.

Course.—It was found that the patient could be relieved quickly of an attack by the administration of glucose intravenously, or by mouth if the symptoms were mild. It was found that the fasting blood sugar varied between 34 and 60 mg. (as determined on 12 consecutive hourly specimens). The blood sugar also seemed to be raised by adrenalin, whole adrenal by mouth, and eschatin hypodermically.

A sugar tolerance test gave the following results:

Fasting	41 mg. per 100 cc.
½ hr.	117 mg. per 100 cc.
1 hr.	86 mg. per 100 cc.
2 hrs.	93 mg. per 100 cc.
3 hrs.	63 mg. per 100 cc.

The patient was put on a high carbohydrate diet (270-42-26) with frequent feedings and remained relatively symptom free. She was transferred to Presbyterian Hospital June 14, 1934, and an exploratory celiotomy was done four days later.

Operation.—June 18, 1934. Spinal anesthesia. A transverse incision was made, exposing the pancreas through the gastrocolic omentum. A tumor about 1 cm. in diameter was removed from the upper border of the pancreas at the junction of the body and the head.

Postoperative Course.—The patient did well and suffered no more attacks. The lowest fasting blood sugar was 115 mg. per 100 cc. She was discharged on the eighteenth day.

Follow Up.—Nine months postoperative. Patient symptom free, no complaints. Scar firm, no hernia. Working at full capacity.

Case III.—E. S. (Presbyterian Unit No. 306695. Neurological Institute No. 3), a white Irish male, 28 years old, was admitted to the Presbyterian Hospital July 13, 1934, complaining of episodes of excitement and maniacal attacks for three years.

Family History.—Essentially negative.

Past History.—Appendicectomy five years ago, followed by phlebitis of left leg. Suprapubic cystostomy for removal of bladder calculus was done three weeks before admission.

Present Illness.—Three years before admission patient began to have attacks somewhat as follows: "Feeling of light-headedness and drawing in arms and legs," with excitement which at times became a real manic episode—tearing his clothes and throwing things around. These last from 30 minutes up to two or three hours. Patient remembers most of the events but is unable to control himself at the time. Mental confusion is marked. They are always worse when fasting, especially early in the morning. The attacks have become more frequent and worse in character, so that now he requires orange juice practically every two hours to ward off attacks.

Patient was admitted to Neurological Institute twice in July, 1931, three years ago. At that time blood studies showed a persistently low sugar, varying from 42 to 75 mg. per 100 cc. He was relatively free from attacks on a high-carbohydrate diet and calories up to 5,000 daily. Since then the patient has been followed in the clinic, and has been given thyroid and pituitary substance with no evident improvement. He has gained about 100 lbs. during this time and now weighs 250 lbs. It is becoming increasingly difficult to ward off the attacks.

Physical Examination.—The patient is a very obese, white male, moderately irritable but fairly coöperative. Temperature, 99.8°; pulse, 60; respirations, 22; blood pressure, 122/80. The only other positive physical findings are moderate hyperactivity of the deep reflexes; palpable liver; right lower quadrant and lower midline abdominal scar.

Laboratory Findings.—Urine, negative. Hemoglobin, 92 per cent; red blood cells, 4,650,000; white blood cells, 5,700; polymorphonuclears, 72 per cent. Wassermann, negative. Roentgen ray of skull: Slight broadening of sella turcica but otherwise normal. Blood amylase, 9.

A sugar tolerance test September 8, 1931, gave the following results:

Fasting	71 mg. per 100 cc.
½ hr.	200 mg. per 100 cc.
1 hr.	150 mg. per 100 cc.
1½ hrs.	187 mg. per 100 cc.
2 hrs.	187 mg. per 100 cc.

The blood sugar showed also a slight rise after injection of 6 cc. of adrenalin (from 76 mg. to 103 mg. in one hour).

Preoperative Course.—During the preoperative stay in this hospital the fasting blood sugars were low, usually about 45 mg. per 100 cc., and at one time 38 mg.

First Operation.—August 13, 1934. Spinal anesthesia. Transverse incision was made, exposing the pancreas through the gastrocolic omentum. A firm, vascular node about 1 cm. in diameter was removed from the inferior border of the pancreas at the junction of the body and head. No other tumors could be felt.

Postoperative Course.—On the morning after operation the blood sugar had fallen to 54 mg. per 100 cc. and later in the day was 47 mg. The patient had no symptoms of hypoglycemia, however, for several days. It was necessary to administer glucose frequently to keep the blood sugar up, but less was needed than before operation. It was felt that a second adenoma had been overlooked, and one month after operation a second exploration was done.

Second Operation.—September 12, 1934. Spinal anesthesia. A tumor in the tail of the pancreas was removed, with six cm. of the tail of the gland. A rubber tube drain was left in. Following this the fasting blood sugar remained normal, the values ranging from 82 to 120 mg. per 100 cc., though one value on the fifth postoperative day was 66 mg. There were no symptoms of hypoglycemia following the second operation.

Postoperative Course.—A pancreatic fistula developed after the last procedure and drained freely, but closed six weeks after operation. The patient has been entirely free from his former hypoglycemic attacks, and his personality changes for the better have been marked.

Follow Up.—Five months postoperative. No recurrence of symptoms. Working regularly 12 hours daily. Scar firm. Fistula closed.

Case IV.—(Presbyterian Unit No. 428308. Neurological Institute No. 4), W. P., a white male jeweler 38 years of age, was admitted to the Presbyterian Hospital August 24, 1934.

Family History.—Negative.

Past History.—Patient has been well except for influenza in 1918. Operation for inguinal hernia was done in 1914.

Present Illness.—In October, 1922, 12 years before admission, patient began to have peculiar attacks of mental confusion and disorientation. The first one occurred while on a long walk, and was accompanied by contraction of the back muscles, so that he walked bent backwards, finally falling to the ground from exhaustion. Since that time the attacks have increased in severity and in number. At first they occurred a few weeks or months apart, but have come on almost every day for the last one to two years, either in mild or severe form. They have assumed varied forms and were considered as epileptic equivalents or petit mal, by the many physicians who saw him. He has become very irritable and fatigues easily, being somewhat drowsy most of the time, and has lost interest in social activities, which formerly he enjoyed. Recently he has had frequent attacks while going home on the train, at times going beyond his station in his confusion and inability to think clearly. Diplopia has been noted several times.

The patient has been admitted to the Neurological Institute four times; in 1926, 1931, 1933, and August 21, 1934. During this time the diagnosis was not made until the last admission. A fasting blood sugar was taken May 27, 1931, and was 83 mg. per 100 cc. (patient had no symptoms when the blood was taken, though he had an attack later in the day). At the last admission, three days ago, the persistent hypoglycemia and relief by glucose were noted and the patient transferred to the Presbyterian Hospital after being studied.

Physical Examination.—The patient is a rather short, well-developed, white male, alert and somewhat anxious. Temperature, 98.6°; pulse, 72; blood pressure, 125/68. The only positive findings physically are slight inequality of the pupils; lack of eye coördination in convergence; and slight tremor of the hands.

Laboratory Findings.—Hemoglobin, 103 per cent; red blood cells, 5,000,000; white blood cells, 6,600; polymorphonuclears, 76 per cent. Blood calcium, 11.0. Blood phosphorus, 2.9. Urine negative. During the previous admissions in the Neurological Institute the patient had been worked up completely as a brain tumor suspect, including spinal puncture and encephalogram. All these studies were negative. A roentgen ray of the skull showed suggestive early Paget's disease. This has not changed over a period of years. The other bones show no changes. Blood sugars on numerous occasions while fasting and during slight attacks have varied from 30 mg. to 60 mg. per 100 cc.

A sugar tolerance test gave the following results:

Fasting	57.5	mg. per 100 cc.
½ hr.	102	mg. per 100 cc.
1 hr.	78	mg. per 100 cc.
2 hrs.	65	mg. per 100 cc.
3 hrs.	68	mg. per 100 cc.

Operation.—August 7, 1934. Spinal anesthesia. Transverse incision. Pancreas explored through gastrocolic omentum. Two tumors were removed—one about 1 cm. in diameter at the lower border of the body, and the other about .6 cm. in the head of the pancreas.

Course.—Recovery was uneventful. The fasting blood sugar varied between 85 and 100 mg., though on the second postoperative day it went down as low as 57 mg. The patient's personality has changed completely, and he explained his feeling "as if a veil had been lifted." He was discharged on the fifteenth day.

Follow Up.—January 23, 1935. Five months postoperative. Patient feels 100 per cent well. Scar linear and well healed. Working at full capacity.

Case V.—H. K. (Presbyterian Unit No. 434384. Neurological Institute No. 5), a white female, 28 years old. First admitted to the Presbyterian Hospital November 30, 1934, complaining of attacks of drowsiness and unconsciousness of six years' duration.

Family History.—One brother died of brain tumor and an aunt has diabetes.

Past History.—Essentially negative.

Present Illness.—Began about six years before admission, and is characterized by a feeling of drowsiness with at times unconsciousness in the early morning. The attacks are preceded by a feeling of mental abnormality, such as irritability and irrelevant remarks. They are relieved by food such as orange juice, and are usually followed by severe headache and perspiration. At times there is diplopia with a feeling of numbness of the extremities. Amnesia is also noted at times, and occasionally incontinence of urine. The attacks were at first about one month apart, but have gradually become more frequent, so that during the past two or three months they have occurred almost daily.

Patient was admitted to Neurological Institute November 12, 1934. A "work-up" was done there and revealed hypoglycemia. The system review is otherwise negative.

Physical Examination.—Between attacks the patient is perfectly normal. Tempera-

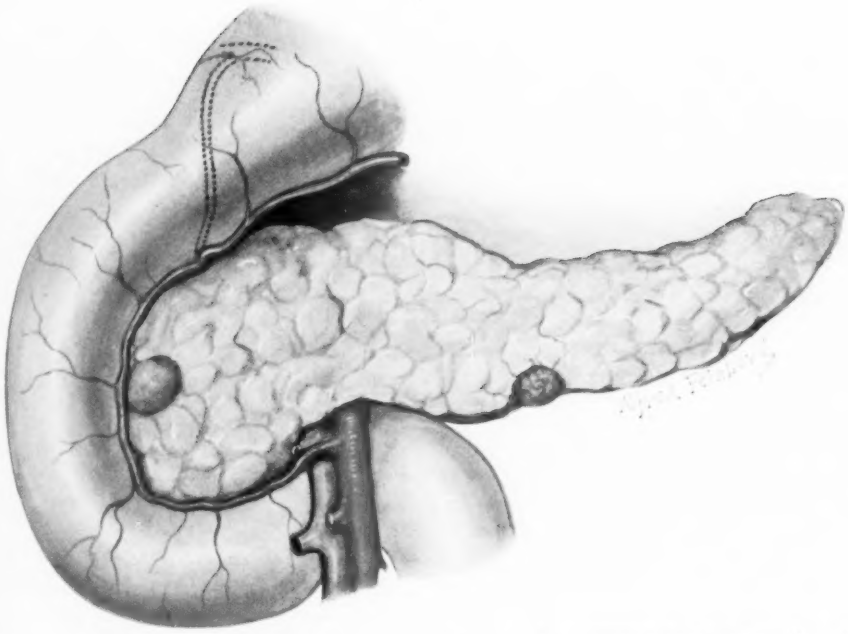

FIG. 13.—The difference in appearance between an adenoma and an enlarged lymph node. Note the richer capillary network over the adenoma at the junction of the body and tail of the pancreas.

ture, 99; pulse, 80; blood pressure, 130/90. The general examination is essentially negative.

Laboratory Data.—Urine, negative. Red blood cells, 4,000,000; hemoglobin, 70 per cent; white blood cells, 9,400; polymorphonuclears, 70 per cent. Wassermann, negative. Roentgen rays of skull and chest, negative. Fasting blood sugar varied between 32 and 65 mg. per 100 cc.

A sugar tolerance test gave the following results:

Fasting	64	mg. per 100 cc.
1 hr.	108	mg. per 100 cc.
1½ hrs.	148	mg. per 100 cc.
2½ hrs.	133	mg. per 100 cc.
Blood amylase	10.9	

Preoperative Course.—Patient was prepared for operation on a high-carbohydrate diet, and transferred to Presbyterian Hospital November 30.

Operation.—Excision of adenoma of pancreas with resection of the tail and part of the body. Spinal anesthesia. Transverse incision just above the umbilicus, with division of both recti muscles. The pancreas was approached through the gastrocolic omentum, and on inspection no tumor could be noted. However, mobilization of the inferior border of the pancreas allowed sufficient palpation so that a tumor could be felt near the junction of the tail and body of the pancreas. Resection of the tail of the pancreas so as to include the tumor was then carried out. A drain was placed in the denudated area and the gastrocolic omentum closed with interrupted silk sutures. The abdomen was also closed in layers with interrupted silk.

Postoperative Course.—Drain removed on the third day, and sutures on the eighth day. Patient's course was entirely uncomplicated. No fistula developed. The blood sugar rose to 220 mg. on the first day, dropped to 110 on the second, and thereafter remained at around 100.

Follow Up.—Four months postoperative. No recurrence of symptoms. No complaints. Scar firm. Working at full capacity.

Case VI.—F. MacD. (Presbyterian Unit No. 350794. Neurological Institute No. 6).

Chief Complaint.—Fainting spells one and a half years' duration.

Family and Personal History.—Negative.

Past History.—General health, good. Acute infectious diseases, negative except for frequent colds to age of 38. Allergic phenomena, negative. Operations or injuries, T and A as a child. Broke coccyx falling down. Head negative. Respiratory negative. Cardiac, occasional slight edema of ankles. Gastrointestinal, negative. Genitourinary, nocturia once always. Menses, leukorrhea. Neuromuscular negative, calm disposition up to present illness. At present cries easily, worries over condition.

Present Illness.—First admission, August 15, 1932. One and a half years ago she began to have uncontrollable dizzy spells. These progressed in severity in a short time to loss of consciousness. There were no prodromata and she remembered nothing of the attack on recovery. They lasted several hours, and were not accompanied by vomiting or craving for food. The attacks occurred at intervals of about one month, usually before or during a regular period. A white vaginal discharge began at this time which was irritating and required the wearing of a pad. Edema of the ankles was more marked after the onset of these attacks. In August, 1932, about one hour after the onset of one of these attacks, she was taken to Neurological Institute where she remained in a semicomatose state for about one week, during which time she developed a left hemiplegia. She had a rapid pulse and fever, her blood sugar was found to be 25 to 38 mg. per 100 cc., and as she did not respond to moderate amounts of intravenous sugar she was referred to the Presbyterian Hospital.

First Admission.—August 15, 1932, to September 6, 1932. Temperature, 99.4°; pulse,

88; respiration, 20; blood pressure, 110/75. Physical examination was essentially negative except for anxious expression, deviation of the tongue to the right, slight weakness on the left, hyperreflexia, left greater than right, positive Babinski, slight edema of ankles, profuse cervical discharge (uterus normal).

Laboratory Findings.—Hemoglobin, 90 per cent; red blood cells, 4,200,000; white blood cells, 11,800; polymorphonuclears, 75 per cent; lymphocytes, 16; mononuclears, 6. Smear, normal.

Glucose tolerance test: 100 Gm. glucose:

Fasting	58 mg.
½ hour	104 mg.
1 hour	130 mg.
2 hours	119 mg.

Cervical smear, no GC found. Urine, normal, Stools, normal. BMR, 13 per cent on two examinations.

Course.—To establish definitely that hypoglycemia was the cause of her attacks she was put on a starvation diet and blood sugars were taken at intervals. The blood sugar dropped to 46 mg. at midnight, at which time she suddenly became comatose. She was given 50 per cent glucose by vein and roused immediately. Thereafter she was put on a high carbohydrate diet (400 Gm.), with much improvement in her general state and some clearing of the hemiplegia. Her blood sugar taken at frequent intervals ranged from 69 to 104 mg. Doctor Whipple was called into consultation and advised operation, but the patient was reluctant to undergo an operative procedure and was discharged on a high carbohydrate diet to be followed in the clinic.

She visited the clinic up to November, 1932, and was improving steadily at that time. She had had no attacks, was following her diet and taking food at night. There was still some residue of the hemiplegia. Her blood sugar was taken at each visit and was 80 ± mg. Operation was urged and her fear of this caused her to stop her visits to the clinic, and put herself under the care of a local doctor.

She returned to the clinic February 8, 1935, with the history of being in good health during the interval, but she had gained 50 pounds and in the last year, in spite of her high carbohydrate diet, she had five or six attacks. Six days before coming in she went without lunch and had had an attack lasting four hours, during which she had had convulsive movements and incontinence of urine. Operation was again urged, and patient was admitted February 14, 1935, for operation for possible adenoma of the pancreas.

Physical Examination on Second Admission.—Temperature, 99.2°; pulse, 88; respiration, 20; blood pressure, 115/75. Obese, healthy, young-looking woman. Mentally alert. Skin, clear. Head, negative. Eyes, negative. Throat, negative. No thyroid enlargement or tracheal deviation. Spine, negative. Lungs, clear. Heart not enlarged, sounds good, no murmurs. Abdomen, negative. Extremities: No tremor, clubbing or edema. Left KJ slightly more active than right. All reflexes hyperactive. No Babinski. Face, symmetrical. Tongue deviates slightly to right.

Operation.—Excision of adenoma of pancreas. February 19, 1935. Spinal pantocaine anesthesia. A characteristic adenoma measuring about 1½ cm. in diameter, having a vascular network, fairly well encapsulated and not difficult to enucleate, was found at the junction of the tail and body of the pancreas. It lay just beneath the splenic artery, which was not damaged in the course of the removal of the adenoma. The rest of the pancreas felt normal and on carefully palpating the head, body and tail for further adenomata nothing resembling an islet neoplasm was felt after the removal of the one described above.

Final Note.—Wound healed by primary union. Silk technic. Patient has been relieved of all her preoperative symptoms, and shows normal blood sugar readings. Home on seventeenth day. Two months: No recurrence of attacks. Blood sugar 102 mg. per 100 cc.

SURGICAL THERAPY

From the study of the reports of the several surgeons who have operated on these cases—some 29 case reports are now available in the literature—and from our own experience in six cases, we offer the following suggestions:

After the diagnosis of chronic hypoglycemia is established and hepatic and pituitary causes have been ruled out, the patient should have a course of medical therapy of three to four weeks to determine the response of the individual to conservative measures. If it is found that the blood sugar values are continuing to remain low, and that the seizures are controlled only on a high-carbohydrate intake, an exploratory celiotomy is indicated.

(1) Spinal pantocaine anesthesia has given us the best operative and postoperative results. Complete relaxation is essential.

(2) A wide transverse incision (Fig. 11), including both recti, provides by far the best approach. We believe a left split rectus fails in the majority of cases to give adequate exposure.

(3) A wide division of the gastrocolic omentum (Fig. 12) exposes the entire pancreas to inspection and palpation—head, body and tail.

(4) The typical gross appearance of the adenoma (Fig. 13) is characterized by a purplish-pink nodule 1 to 2 cm. in diameter, usually standing out distinctly from the whiter pancreatic tissue, and covered with fine vessels which bleed easily, but are readily ligated. The adenoma is usually encapsulated, and is shelled out without difficulty after the small vessels have been ligated with the finest of silk ligatures.

(5) If one adenoma is discovered, search should be made for others. If no adenoma or adenomata are seen on the anterior surface, the pancreas should be mobilized by incising its inferior peritoneal attachment and gently elevated, inspected and palpated on its posterior aspect. Hemorrhage is most apt to occur around the head.

(6) Adenomata are most frequently found in the tail and body, and should be looked for in these areas first.

(7) If no adenoma or adenomata can be seen or felt, the next most effective measure is the removal of at least two-thirds of the pancreas—that is, the tail and body—leaving the portion of the head in the curvature of the duodenum. Doctor Thomason in a personal communication says that in his operation he followed the suggestion of Dr. Emil Holman, of San Francisco, who stated that if he had another case to do he would ligate the splenic artery, because of the difficulty in dealing with the bleeding of its branches going into the pancreas. Doctor Thomason did this, which of course necessitated a splenectomy as well, but the ligation of the splenic artery rendered the operation practically bloodless, and the mechanical features were greatly simplified. He removed the tail and body, excising the pancreas with a Percy cautery, searing the end very thoroughly. A Penrose drain was used, but there was no discharge and the patient made an absolutely uninterrupted recovery with primary wound healing.

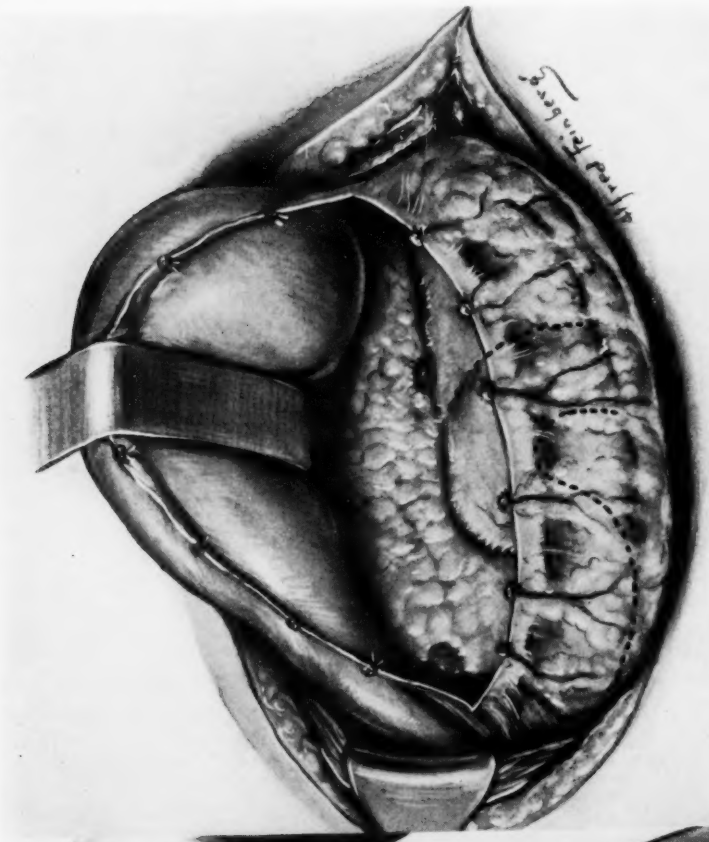

FIG. 12.—Exposure of the lesser sac, with head, body and tail visualized by incising through gastrocolic omentum.

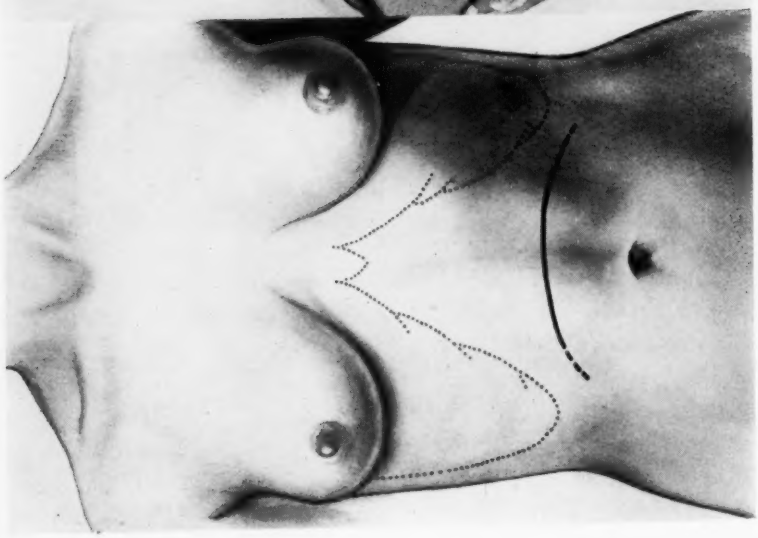

FIG. 11.—The site and type of transverse incision used in exploring a tumor of the pancreas.

(8) A drain should be placed down to the bed of the pancreas, if the organ is resected, to provide for oozing or a leakage of pancreatic juice. As a rule, the site of an enucleated adenoma does not have to be drained.

(9) Silk technic, using the finest grade of silk for ligatures of small vessels and a slightly heavier grade for the larger vessels and the rectus sheaths, has given us perfect wound repair.

The test of any therapy is the final result. In the reported cases, including the six of our own, there have been no fatalities. All of the patients from whom adenomata have been removed have been cured their hypoglycemia. In the cases treated medically there has been no proof that the hypoglycemia was due to adenoma of the islet cells. Because of the deep-seated lesions and the important structures involved, the operation should not be attempted by surgons who are not experienced in the anatomy and surgery of the pancreas.

CONCLUSIONS

We have reviewed the study of the pancreas from the viewpoint of its endocrine function, have tabulated the cases of hypoglycemia and of island cell tumor, so far as we have been able to find them reported, have presented our study of eight tumors, and have outlined the surgical therapy of these lesions.

NOTE.—We are indebted to Dr. George F. Laidlaw for countless microscopic preparations with special stains; to Miss Schramm of the Janeway Library for her assistance in obtaining the bibliographic references, and to Dr. Arthur P. Stout for his advice in interpreting the histology.

Since this article has been in press Doctor Laidlaw reports further progress in granule stains as follows: "The tumor cells are filled with fine granules resembling the granulation of normal island cells. As in normal islands, most of the tumor cells resemble the so-called beta cells, with here and there a single cell or a small group of cells resembling an alpha cell." A more detailed study of the histology will appear later.

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SUBTOTAL PANCREATECTOMY FOR HYPERINSULINISM

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SINCE the year 1927, when the first case of hyperinsulinism to be explored surgically was reported by Wilder, *et al,* [23] approximately 26 of these patients, according to the literature, have been subjected to surgical intervention. In six of the cases, definite adenomatous nodules, composed of islet cells, were encountered and enucleated without particular difficulty; but in fourteen of the remaining patients, no tumor of the pancreas could be found after careful inspection and palpation, and in these patients, the operators generally endeavored to resect greater or lesser amounts of pancreatic tissue. The greatest amount reported to have been removed thus far has been 60 Gm. and the smallest amount, five Gm. In general, greater improvement has resulted in cases in which definite, discrete tumor nodules have been discovered and removed. Whether such discrete lesions are invariably present, though not detectable because deeply buried, or whether the lesions may sometimes be of a diffuse type, with numerical increase in the Islands of Langerhans or hypertrophy and hyperplasia of its cellular components, is not yet known with certainty.

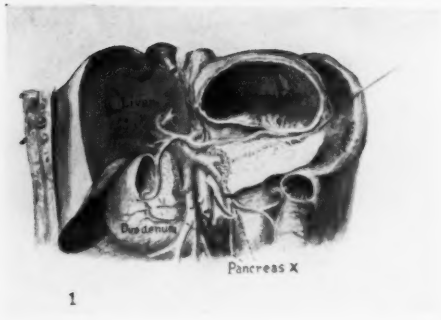
The number of cases of hyperinsulinism being recognized by clinicians everywhere, particularly the milder forms, appears to be on the increase,[3, 4, 5, 20] but only a small number of these are severe enough to require exploration of the pancreas. It is of great importance that cases for surgical treatment be selected only after very careful clinical study. The differentiation, if possible, of the hypoglycemias of extrapancreatic origin is most desirable.[2, 6, 7, 8, 11, 13, 18, 24]

If Wilder's supposition that some hypoglycemic states may be analogous to certain hyperthyroid conditions be true, then it will obviously be necessary to resect much more of the pancreas than has been done in the majority of cases thus far reported in the literature. The clinical improvement which has followed ample resections in patients in whom the resected portion of pancreas has been described by pathologists as apparently normal on microscopic study and in which tumors have not been found, is at least significant. In the case of subtotal thyroidectomy for hyperthyroidism, the necessity for the resection of at least 50 per cent of each lobe in order to obtain improvement or cure is a well recognized principle and, indeed, most operators usually remove a much greater proportion than this. While it is as yet too early to predict the ultimate value of pancreatic surgery in the severer cases of hyperinsulinism, the number of these patients now being subjected to operative treatment is increas-

ing and there is a need for further clarification of the technical problems involved in resection of the pancreas.

In my experience the following technic has proved of value in simplifying the procedure. Shortly before operation, the patient is given 500 cc. of a 10 per cent solution of glucose intravenously and the stomach is thoroughly emptied of fluid and gas by aspiration. The preliminary medication consists of morphine sulphate gr. 1/6 (.0108 Gm.) and atropine sulphate gr. 1/150 (.0004 Gm.) given hypodermically. Ether anesthesia is used by preference because of its reputed effect in sustaining and even elevating the normal level of the blood sugar. This point has been disputed by some but in a series of observations on two of my own cases in which blood sugar determinations were made from the time of the beginning of the anesthesia and repeated at frequent intervals during the operation, particularly during those stages in which the pancreas was being most actively manipulated, the maintenance of a satisfactory level of blood sugar throughout was demonstrated.

The technic is best shown in the accompanying drawings (Figs. 1, 2*a* and *b*, 3*a* and *b*, 4*a* and *b* and 5). A long left midrectus incision is made. I have not found it necessary to make either the T or the transverse type of incision recommended by some.[10, 21] Four avenues of approach to the body and tail of the pancreas have been described, but of these only two, namely, that through the gastrohepatic omentum and that by way of the gastrocolic omentum, are of much value. The latter approach would in most instances seem superior and it is the only one which I have so far employed. The gastrocolic omentum is divided transversely and a large gauze pack is placed against the stomach which is rotated slightly and drawn upward by the hand of an assistant. A second pack is placed over the transverse colon which is then displaced downward by the assistant's other hand. The abdominal walls are retracted laterally. The excellent exposure thus obtained is shown in the illustrations. The next important step is the elevation of the small of the back which may be secured by means of the ordinary operating table backrest. This brings the pancreas forward to a surprising degree and increases the accessibility of the body and tail considerably. The resection is begun by dividing the peritoneal investment along the lower margin of the pancreas and grasping the tail with a suitable holding forcep and drawing it slightly forward and downward. The most important step in the operation now follows and consists in the passing of temporary tape ligatures about the splenic vein and splenic artery. The pancreas is far more intimately attached to these vessels, particularly the vein, than illustrations in most text-books and atlases of anatomy would lead one to expect. Hence, this maneuver serves a double purpose in the subsequent dissection which is directed toward the freeing of the tail and the body of the pancreas from the splenic artery and vein because it not only enables one by traction and countertraction to display the numerous tributary vessels supplying the tail and body of the pancreas by placing them on a stretch, but it also gives immediate control of the vascular



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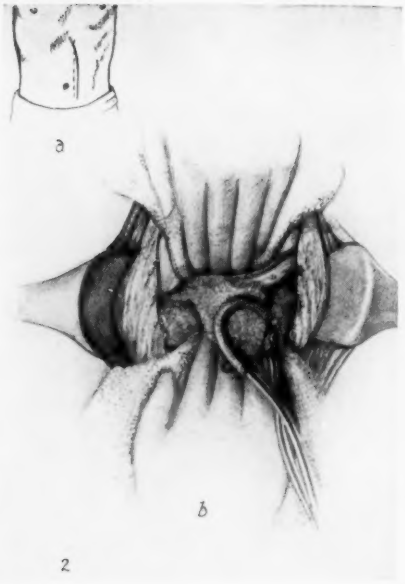

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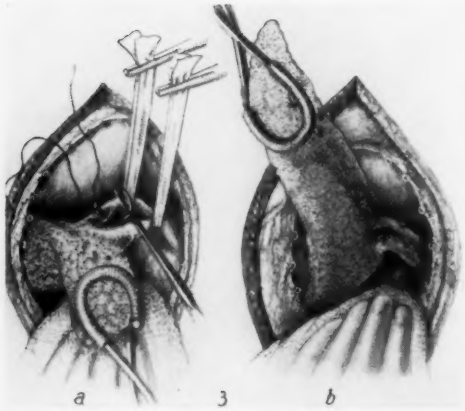

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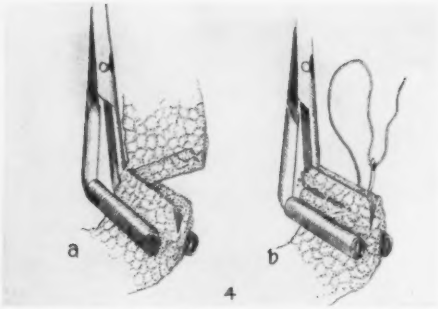

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FIG. 1.—The surgical anatomy of the pancreas modified from Spalteholz. Note the intimate relation of the body of the pancreas and the splenic vein also the numerous tributary vessels of the splenic artery and vein.

FIG. 2.—(*a*) The location of the incision. (*b*) The exposure obtained through the gastrocolic omentum. The tail of the pancreas is drawn forward by means of a rubber guarded Collins common duct forcep.

FIG. 3.—(*a*) Traction and countertraction with the temporary tape ligatures and the Collins forcep discloses the tributary vessels by placing them on the stretch. An aneurysm needle is shown introducing the ligatures. (*b*) The numerous small venous and arterial branches have been ligated and divided, and the pancreas is shown dislodged from its bed.

FIG. 4.—(*a*) The pancreas is now grasped with a rubber covered right angle forcep to steady it and control bleeding during the resection and suture of the stump. A V-shaped type of incision divides the body at the point of election. (*b*) Suture of the pancreas with a running mattress and return lock stitch is begun.

FIG. 5.—The final appearance of the operative field. The suture of the pancreas has been completed. A rubber tissue drain is placed to the bed of the excised portion of the pancreas.

pedicle of the spleen should either vein or artery be inadvertently wounded. The task of separating the splenic vein and artery from the adherent pancreatic tissue is somewhat tedious but with patience it may be accomplished without particular difficulty. The technic is not unlike that used in experimental surgery in the performance of total pancreatectomy in dogs. The tributary vessels may be divided between ligatures, using either an aneurysm needle or an artery forcep to introduce the suture underneath the vessel. These vessels are for the most part quite small in relation to the size of the parent vessel but bleeding is apt to be quite troublesome if they are not adequately secured. One fairly large artery, the *pancreatica magna*, enters the distal portion of the body and should be secured early in the dissection.

The dissection is continued until the region of the junction of the body with the head is reached. One may then remove as much of the gland as seems indicated by the severity of the case at hand. There are as yet, however, no conclusive data correlating the severity of the symptoms with the degree of relief obtained following the resection of varying amounts of the gland, but it has been stated that one may remove as much as 90 per cent of the pancreas without producing permanent glycosuria.[12, 21] I have not found it necessary to apply crushing clamps as advocated by some[1, 21] but have preferred to have an assistant hold the body of the pancreas in the grasp of a rubber covered right angle forcep, just tightly enough to control bleeding. The pancreas may then be divided with a V type of incision and the stump closed with either an interrupted mattress suture or running lock stitch as shown in the sketch. This method of dealing with the stump gives very satisfactory hemostasis. A rubber tissue drain is introduced to the bed of the resected portion and the gastrocolic omentum is closed loosely about the drain. The omission of drainage in these cases is only to invite trouble. In one of my patients, I removed the drain on the 14th day after operation and within 48 hours he experienced severe pain and tenderness in the left hypochondrium, a considerable elevation in temperature, and a leukocytosis of 29,000. This patient, until this occurred, had had an otherwise uneventful convalescence. After about 72 hours, there was a sudden gush of dark brown, odorless fluid from the drainage tract and the patient's condition improved promptly. Others have reported similar experiences in drained cases and at least two undrained cases have required secondary operations for removal of fluid accumulations in the lesser peritoneal cavity.

After operation, the pancreatectomized patient may be treated much as any other laparotomy case, except that the blood sugar should be maintained at normal levels by the administration of carbohydrates as indicated. The management of the pancreatic fistulae which have occurred in a large number of the cases reported should present no particular difficulty provided infection is absent. The majority of these fistulae have closed spontaneously after a time. Pancreatic juice as it comes directly from the gland is not proteolytic to any degree,[9, 15, 16, 17, 19] and should cause no digestion about the wound.

If the juice becomes infected, however, it will cause a marked reaction and all the various measures recommended for protecting the adjacent tissues against the digestive action of activated pancreatic juice may have to be utilized.

The deliberate sacrifice of the spleen as a measure for simplifying the operative procedure by allowing the removal of its vascular pedicle *en bloc* with the segment of pancreas has been advocated,[14, 22] but I believe that with care and patience the resection can be accomplished as I have described without recourse to this maneuver; and unless these vessels are accidentally wounded, their ligation and consequent splenectomy should not be necessary.

It is of interest that so far no fatalities attributable to the operation itself have been reported in the literature. This is particularly encouraging because the pancreas for many years has been considered an organ beyond the scope of ordinary surgical attack.

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THE SURGICAL TREATMENT OF CHRONIC PANCREATITIS*

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A BARE generation ago, chronic pancreatitis was considered a rarity—or its entity denied by internists. Opie[11] taught that its symptoms were so indefinite as to make it impossible of preoperative diagnosis *intra vitam.* Fitz in this country, Moynihan and Mayo-Robson in England, took the opposite view, claiming that careful study of the patient's history, supplemented by chemical and microscopic examination of the excreta should enable one to make a correct diagnosis in a majority of cases. Somewhere between these two extremes lies the truth.

As clinicians began to grasp the all-important fact of the close interrelation which exists between the liver and its biliary tract on the one hand and the pancreas with its ducts on the other, dysfunctions of the latter organ began to assume greater importance. In disturbances of a gland having such varied and all-important functions as has the pancreas one would—*a priori*—be justified in assuming that clinical revelations would be many and almost pathognomonic. Unfortunately, the only two striking clinical manifestations are fat necrosis and pancreatic hemorrhage, both present in the severest of cases, both demonstrable only at the time of surgical intervention.

Every clinician of note, both in the United States and Europe, has, one or more times in his career, written on gallbladder disease. *Per contra,* rare are the analyses of pancreatic dysfunction yet, biologically, anatomically and physiologically the pancreas cannot be separated from the biliary tract of which it forms a component part. With the exception of acute hemorrhagic pancreatitis and carcinoma of the head of the pancreas, surgical intervention in cases of subacute or chronic pancreatitis has not claimed the attention which these dysfunctions demand. This neglect must, in part at least, be attributed to the popularity of indiscriminate cholecystectomy but more especially to the paucity of symptoms by means of which the clinician can make a tentative preoperative diagnosis. Rutherford Morrison once wrote that "If the history, symptoms and signs do not exactly fit acute intestinal obstruction, or stomach or duodenal perforation, perforated appendix or acute cholecystitis, and yet have some resemblance to each of them, pancreatitis is the most probable cause." He was, of course, referring to pancreatic apoplexy, but his remarks apply equally well to chronic pancreatitis. Gosset and Petit-Dutaillis[2] are of the opinion that there is nothing harder to do in medicine than to describe a precise symptomatology of chronic pancreatitis. Symptoms

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when present are often "borrowed" from compression of neighboring organs. It is a mistake, said Deaver,[8] to lay too much stress on the laboratory means of diagnosis in the recognition of chronic pancreatitis. It remains a diagnosis to be made from grosser observations of symptoms and signs, with a reasoned conclusion from the probabilities of the case. In the majority of cases exploration alone will decide. The percentage of diagnoses of chronic pancreatitis varies widely in different clinics, even at the time of operation (Mayo-Robson 65, Deaver 35, Kehr 30, Mayo Clinic 6.1 per cent). M. Matthes[3] comes nearer the truth than any other writer we have had access to when he states that "In the majority of cases the diagnosis of diseases of the pancreas depends, not upon the individual symptom but upon the grouping of the symptom complex. Individual symptoms of the pancreas resemble symptoms of other gastro-intestinal diseases, and the most diagnostic characteristic of diseases of the pancreas is brought about by the effect the diseased pancreas has on its neighboring organs."

Dyspepsia (a much abused and vague term), fat intolerance, epigastric pain, alternating constipation and diarrhea and the so-called "butter stool"—a muddy stool covered with a layer of fat which gives it a buttery appearance—all tend to confirm Matthes' statement. Much can often be learned through gross and sometimes microscopic or cultural examination of feces; modern plumbing is causing this diagnostic test to become almost obsolete.

Clinically, pancreatic dysfunctions can be divided into three main groups: (*a*) disturbances of external secretion interfering with the digestive apparatus in the subacute or chronic types, or producing autolysis in the fulminating cases of pancreatic apoplexy; (*b*) disturbances of internal secretion leading to glycosuria; and (*c*) carcinoma of the head of the pancreas.

The only surgical case involving both internal and external pancreatic secretions in our series is as follows:

Case Report.—No. 70265, Ravenswood Hospital, referred to us by Dr. W. K. Yeakel. A 53-year-old man was suddenly seized with severe epigastric pain, nausea and emesis. Glycosuria had been present for the previous five years, readily controlled by diet and insulin. The patient was a robust looking individual, weighing about 170 pounds and not appearing acutely ill. Fixed epigastric pain and tenderness just above and to the left of the umbilicus were present with a moderate degree of abdominal distention and marked bilateral rectus rigidity, more accentuated in the upper abdominal quadrants. He was not in shock. A working diagnosis of subacute pancreatitis was made. On admission his temperature was 102°, pulse 90, respirations 20. His blood count showed five million reds, 16,500 whites, of which 71 per cent were mature neutrophiles, 16 per cent immature, and 13 per cent mononuclears or transitionals. Urinalysis showed a trace of albumin and complete sugar reduction. At operation fat necrosis of omentum was present, acute hepatitis, an enlarged, boggy head of the pancreas and inspissated bile in an overdistended gallbladder. No biliary calculi were found in either gallbladder or biliary ducts. The gallbladder was drained. Patient's condition at the end of the operation was excellent and he gave us no anxiety for the first twenty-four hours. Twenty minims of insulin were given on the second postoperative day. He became very restless, vomited frequently, developed involuntary urination and defecation and his pulse rate increased to 120–150 before exitus on the third postoperative day. A necropsy of

this interesting case unfortunately was not obtainable and one can only speculate regarding the relative importance of the etiologic factors involved. Was this an insulin death, or did the subacute pancreatitis become hemorrhagic postoperatively?

As a preliminary basis for our study we reviewed 50 cases of pancreatic disease referred to surgical services. Of these, 18 were from our Cook County service (1927–1931) and 32 from the surgical service of Ravenswood Hospital. To this original survey have been added 17 cases of chronic pancreatitis, a total of 30 cases which we have analysed in this presentation.

The youngest patient in this series was a six-year-old girl, the oldest 83. Seventy per cent of our patients had attained or passed their sixtieth year. As a majority of them gave a history strongly suggestive of pancreatic dysfunction covering a period of years, we fully agree with the late Sir William Osler that most of these patients seek relief in the fourth to sixth decades of life. Contrary to other statistics, 67 per cent of our patients were females, 33 per cent males. Bohm, Deaver and Opie reported that 65, 58 and 66 per cent of their patients were males.

Our original series of fifty cases may be classified into four groups:

1. Carcinoma of the head of the pancreas		25 cases (50 per cent)
2. Acute pancreatitis		8 cases (16 per cent)
	Hemorrhagic 4	
	Gangrenous 2	
	Catarrhal (?) 1	
	Diabetic 1	
3. Chronic pancreatitis		13 cases (26 per cent)
4. Undetermined		4 cases (8 per cent)

The known mortality of the carcinoma cases was 76 per cent, of the pancreatic apoplexy cases 50 per cent, undetermined cases 25 per cent and no mortality in the thirteen cases of chronic pancreatitis. That the ultimate mortality of our carcinoma cases reached 100 per cent is, of course, conceded.

Case Reports

Case No. 68046, Ravenswood Hospital, seems worthy of special mention. A six-year-old girl, referred to us by Dr. M. R. Breck, gave a history of having suffered from two or three vomiting spells yearly since the age of four. The quality and quantity of food allowed apparently bore no relation to these attacks. Previously admitted to the hospital in 1932, she had been under medical observation without any definite diagnosis having been concurred in. When seen in consultation with Doctor Breck in January, 1933, the child had been suffering for the past several days with severe intermittent upper abdominal pains associated with nausea and emesis. Routine "work-up" was negative with the exception of bile in the urine. No icterus was present. Peristaltic waves could not be determined. A preoperative diagnosis of pyloric stenosis was made and operative intervention advised. On opening the peritoneal cavity through an upper paramedian incision, extensive fat necrosis of the omentum was revealed with easily separable adhesions about the pylorus, gallbladder, duodenum and transverse colon. The gallbladder appeared normal and no gallstones in the gallbladder or common duct were palpable. The pylorus and a portion of the lesser curvature were markedly hypertrophied and acutely edematous; the head of the pancreas felt acutely congested and boggy. Owing to the extent of the lesser curvature involvement it was felt that a simple pyloroplasty

would not give the desired relief and a rapid posterior gastro-enterostomy was performed. The gallbladder was not drained in this case for two reasons: we believed that the pyloric stenosis was responsible for the subacute pancreatitis and, also, that the little patient would not stand a double operation. The abdomen was closed without drainage. She made an uneventful recovery and her parents have periodically reported that she has remained in excellent good health for over two years.

The etiologic sequence of events in this very unusual case is rather difficult of interpretation. Did the edema of the head of the pancreas create the peripyloric adhesions and thus tend to bring about a progressive hypertrophy of the pylorus and lesser curvature? Our feeling at the time of operation was that, by relieving the pyloric stenosis, the pancreatic edema would subside.

The case which stimulated us more than any other in our endeavor to diagnose chronic pancreatitis preoperatively was No. 66615, Ravenswood Hospital, referred by Dr. J. H. Kincaid in September, 1932. A female patient, aged 60, had been under her physician's observation for over five months, her essential complaints being pain in the right upper abdominal quadrant, nausea, vomiting, and a loss of 20 pounds in weight. Blood examination and urinalysis were essentially negative. Her liver was palpable below the costal arch but not particularly tender. Cholecystography was indeterminate: "The gallbladder cannot be definitely outlined. There is a shadow having the appearance of a gallbladder which is probably due to thickening of its walls."

An exploratory laparotomy was advised with a tentative preoperative diagnosis of carcinoma of the head of the pancreas, in spite of the absence of icterus but largely on account of the age, vague findings and subcachectic appearance of the patient. On opening the upper abdomen the liver was found to extend one inch below the costal arch. Rather dense adhesions between the liver and duodenum were encountered and freed. The duodenum was markedly dilated and distorted. The head of the pancreas was enlarged, hardened, but not nodular. No fat necrosis was present. The common duct was free of stones and normal in size. The cystic duct was less than one inch long, markedly dilated and slightly mushroom shaped. There was no gallbladder! Cholecystodochotomy was performed. The patient made an easy recovery; the drainage tube was removed on the tenth day and the fistula closed in about six weeks. Two and a half years have elapsed since the operation. The patient has remained in fairly good health during this period, long enough to exclude carcinoma and to class the case definitely as one of congenital absence of the gallbladder with chronic pancreatitis.

Anatomic Considerations.—The morphology of the pancreas is only very briefly alluded to in order to reemphasize the close interrelation which exists between it and the duodenum, stomach and biliary tract. This gland is developed from two processes which arise from the second part of the duodenum. One process, which forms the lower part of the head of the pancreas, springs from the ventral aspect of the duodenum in common with the hepatic diverticulum, but later, on account of the rotation of the duodenum, comes to lie on the dorsal aspect of the other process. The second process arises from the dorsal aspect of the duodenum, passes into the dorsal mesogastrium to the spleen, and ultimately forms the greater part of the gland. Two anlages form the ducts; the ventral one develops into the duct of Wirsung while the dorsal anlage becomes the accessory duct of Santorini. Both ducts usually join and after their junction the duct of Santorini usually ceases to open into the duodenum; in some cases, however, both ducts open into the duodenum. The head of the pancreas is almost completely sur-

rounded by the duodenum. The anterior surface of the pancreas is separated from the stomach and colon by the lesser peritoneal cavity. A part of the general peritoneal cavity impinges against the antero-inferior angle of the gland. Closely hugging the head of the pancreas and often imbedded in it is the common bile duct. The gland has no true capsule, in the anatomic sense of the term. The structure that is divided on incision into the pancreas is the peritoneum covering the organ on its antero-inferior aspect. An incision through this peritoneal covering cannot relieve glandular tension. In order to actually relieve the pressure tension in the pancreas—as pointed out by Mikklesen[1]—it would be necessary to divide the thin layer of connective tissue covering each lobule—a surgical impossibility. Cameron and Noble[9] found that a common channel of the ductus communis and ductus pancreaticus is present in 74 per cent of humans and that, in 66 per cent of cases, blockage of the ampulla of Vater caused diversion of bile into the pancreatic duct.

Etiology.—That chronic pancreatitis must be the resultant of repeated attacks of acute subsiding pancreatitis is self-evident. Is pancreatitis the primary lesion or does it follow a lesion of the biliary tract or of a contiguous organ such as the stomach or duodenum? Retrograde infection of the pancreas through the lymphatics from the gallbladder, appendix or a duodenal ulcer, though upheld by Mangerot, Arnsperger, Franke, Bartels, Sweet, Kauffman and others, is now regarded as extremely improbable. Pancreatic calculi, gradually blocking one or both excretory ducts, are so rare as to be surgical curiosities; only about one hundred cases are on record to date (Stevens[4]). The hematogenous route, though possibly explaining some of the fulminating cases of acute hemorrhagic pancreatitis, can be rejected insofar as chronic pancreatitis is concerned.

Direct continuity as an etiologic factor plays an occasional rôle. Hurst and Stewart[6] reported that in 233 autopsies on patients having succumbed to gastric or duodenal ulcers, the pancreas formed the floor of the ulcer in 25 per cent of all cases; also that in the performance of 183 partial gastrectomies the pancreas formed the floor of the ulcer in 20 per cent of all cases. May not some of our clinical failures in peptic or duodenal ulcer cases be due to the nonrecognition and nontreatment of a chronic pancreatitis which was overlooked.? Dyas[7] has called our attention to duodenal stasis as an occasional factor in biliary tract disease. We have, so far, not encountered or failed to recognize a congenital stenosis of the duodenum but have found and freed adhesions associated with marked dilatation of the duodenum which we felt contributed to the syndrome of chronic pancreatitis.

We believe that repeated, subsiding attacks of pancreatitis are, at least in the vast majority of cases, due to the entrance of bile into the pancreatic duct or ducts. We furthermore believe that, as long as normal bile from the gallbladder is discharged through the common duct into the duodenum, no pancreatitis will result. The work of Opie, Flexner, Archibald,[10] Nordman, Cameron and Noble has shown that: (*a*) bile plus gallbladder mucin does

not inflame the pancreas; (*b*) pure liver bile (blocked cystic duct) causes pancreatitis; (*c*) infected bile (cholecystitis) causes pancreatitis.

If the gallbladder is congenitally absent, has been previously removed by operation or its cystic duct has become blocked by stone or other pathologic process, the hepatic and common ducts may not be able to dilate sufficiently to compensate for increased pressure changes. The normal secreting pressure in the biliary system is approximately 200 Mm.; if raised to 500 Mm., retrojection of bile (minus gallbladder mucin) into the pancreatic duct may occur. Clinical reports of bile diversion into the pancreas have been published by Halsted, Körte, Ebner, Egdahl, Mayo-Robson, Moynihan and others.

We are of the opinion that chronic pancreatitis is the resultant either of cholelithiasis with blockage of the cystic duct or of cholecystitis of sufficient severity either to interfere with mucin formation or to destroy gallbladder mucosa. Blockage of the ampulla of Vater will produce the same result if cholecystitis is present. Our own cases speak overwhelmingly for cholecystitis as the principal factor (27 cases), only one case having a stone in the cystic duct. According to Opie, chronic pancreatitis is caused by biliary infection extending into the pancreas, either because of obstruction at the ampulla or directly. Small amounts of bile enter the pancreas at frequent intervals (repeated subsiding acute pancreatitis), and produce chronic inflammation and subsequent fibrosis. In addition, arteriosclerosis, cysts or tumors of the pancreas, alcoholism, tuberculosis, syphilis, hemochromatosis and hepatic cirrhosis seem to be possible etiologic factors.

Symptoms and Diagnosis.—As disturbances of the internal secretion of the pancreas do not—except remotely—belong to the domain of surgery, no mention of its symptomatology is considered here. There are no pathognomonic signs or symptoms peculiar to chronic pancreatitis; broadly speaking, one may state that the general picture is one of biliary tract stasis, the chief offending portion of this complex tract being the gallbladder, cystic duct or ampulla of Vater—mentioned in their clinical order of frequence. In our analysis of the thirty cases we have had the opportunity of studying we found the following departures from normal (TABLE I):

TABLE I

	Per cent
Dyspepsia	85
Pain and tenderness in R. U. Q.	55
Nausea and emesis	34
Weakness and anorexia	24
Bile in urine	18
Icterus (slight)	16
Icterus (severe)	12
Anasarca	12
Chronic constipation	10
Enlarged liver	8
Chills and fever	4
Clay stools	2

With such a vague picture to study from it is not surprising that a diagnosis of chronic pancreatitis can be made only by a careful process of exclusion. It is chiefly by means of negative findings that one can preoperatively orient oneself in the right direction. With no history of biliary colic, of persistent or remittent icterus; with cholecystography negative as to calculi; with nonvisualization or weak visualization of the gallbladder one should, at least, suspect the possibility of chronic pancreatitis. J. W. Hinton[5] is quite correct in stating that "the pancreas is the only intra-abdominal organ that produces symptoms of a chronic surgical nature that physical examination, roentgenologic or laboratory studies will not aid in establishing a diagnosis except by negative findings." J. M. T. Finney is of the opinion that, even in the rare cases of pancreatic calculi, there is no distinctive clinical picture upon which to base a diagnosis. Laboratory aids in diagnosis such as Schmidt's test meal (small pieces of meat, hardened in alcohol and placed in a gauze bag which is swallowed by the patient), Ehrmann's test (based on the fact that neutral fat, free from fatty acid, is split by the lipase from the pancreas, the resulting acid forming green salts with copper), the Cammidge test (salol liberating carbolic acid), the Opie-Hewlett lipase test in the urine, Sahli's glucoid capsule test and Schmidt's test diet are all too time consuming and too uncertain to warrant their routine use. According to Archibald, the simple test for hyperglycemia is the only one worth retaining, even though the raised blood sugar is present only in the first two or three days of an attack. He adds, however, that the Loëwi pupillary reaction test (adrenalin dropped in the eye causes mydriasis if pancreatitis is present—and hyperthyroidism is absent), is of some value although its negative result does not exclude pancreatitis.

In our series of cases we have not resorted to any special laboratory tests and hence cannot speak for or against them. The preoperative working diagnosis in thirty cases credits us with an accuracy of 10 per cent, slightly better than that of Robert Elman (8 per cent).

TABLE II

Preoperative Diagnosis in 30 Cases (Tarnowsky-Sarma)

	Cases	Per cent
Carcinoma of head of pancreas	10	33.3
Chronic cholecystitis (noncalculous)	8	26.6
Cholelithiasis	5	16.6
Chronic pancreatitis	3	10.0
Pyloric stenosis (six-year-old girl)	1	3.5
No working diagnosis (exploratory)	3	10.0

Archibald states that, out of eleven cases of chronic pancreatitis reported some years ago he was able to make a correct preoperative diagnosis in seven of them (63 per cent).

TABLE III

Preoperative Working Diagnosis in 37 Cases of Recurrent Pancreatitis (Robert Elman)

	Cases	Per cent
Cholecystitis	7	18.9
Intestinal obstruction	6	16.2
Perforated ulcer	9	24.4
Duodenal ulcer	2	5.4
Appendicitis	1	2.7
Hepatic abscess	1	2.7
Perforated gallbladder	1	2.7
No working diagnosis	7	18.9
Recurrent pancreatitis	3	8.0

What, in our opinion, is much more important is the recognition of an enlargement and engorgement of the head of the pancreas at the time of operation. We have no yardstick for estimating the size or tension of a Riedel's tumor; experience alone will enable the surgeon to arrive at a correct interpretation. Repeated palpation of very recent postmortem specimens in the morgue or of fresh sweetbreads in the stockyards is an invaluable aid. The greatest difficulty lies in differentiating by palpation an early, preicteric carcinoma of the head of the pancreas and chronic pancreatitis. A close follow up has enabled us to revise our operative diagnosis in several cases. The typical carcinoma of the pancreas is nodular; the typical chronic pancreatitis is tense but smooth—there are unfortunately exceptions to this rule. Our chart of operative findings gives a graphic picture of long existing inflammation of the biliary tract with enlargement of the head of the pancreas recognized in 75 per cent of all cases. Fat necrosis was present in only two cases (TABLE IV). Why it should occur is not clear even in the minds of physiologists who suggest that it may be due to either escape of gland secretion or to dissemination of a fat-splitting ferment from the pancreas through the lymphatics.

TABLE IV

Operative Findings in 30 Cases of Chronic Pancreatitis

	Cases	Per cent
Enlarged liver	27	90.0
Enlarged head of pancreas	22	75.0
Adhesions	21	70.0
Hydrops of gallbladder	3	10.0
Dilatation of biliary ducts	2	7.0
Fat necrosis of omentum	2	7.0
Duodenal stasis (adhesions)	1	3.3
Gallstones in gallbladder	1	3.3
Congenital absence of gallbladder	1	3.3
Stones in biliary ducts	None	0.0

Pathology.—Adhesions of varying density and extent were present in 21 of our cases (70 per cent). We have, to date, no personal report on morbid

anatomy of the pancreas to report. The comparatively few postmortem examinations of the pancreas on record all concur in limiting pathologic changes to the interlobular septa and parenchyma of external secretion. Deaver was inclined to ascribe the pathologic changes to retroperitoneal infection involving more especially the so called triangle of infection or that portion of the head of the pancreas bounded by the ducts of Wirsung and Santorini. This particular area has an abundant lymphatic system closely connected with the intestinal tract. Opie stated that chronic pancreatitis was a disease of its stroma. Macroscopically one finds accentuated lobulation of the glands through the increase of connective tissue. The lobules themselves are invaded by newly formed stroma and may be in various degrees of disintegration or replacement. The main ducts show dilatation and the cells of the alveoli become atrophic.

Treatment.—Cholecystostomy with prolonged drainage is the operation of choice in chronic pancreatitis (TABLE V). It is rare to find such unanimity in surgical literature! Gask, Mayo-Robson, Moynihan, Cammidge, Gosset, Petit-Dutaillis, Hartman, Hey-Grove, Deaver, Finney, Horsley, Archibald, Cecil, Osler and others, all make the same recommendation.

TABLE V

Operative Procedure in 30 Cases

	Cases	Per cent
Freeing of adhesions and cholecystostomy...	25	83.5
Freeing of adhesions and post.-gast.-ent.....	2	6.6
Freeing of adhesions and choledochotomy (congenital absence of gallbladder).....	1	3.3
Exploratory laparotomy (no drainage of gallbladder).....	2	6.6

We submit that many patients on whom a cholecystectomy had been performed without giving them more than temporary relief may in reality have been suffering from an unrecognized chronic pancreatitis for the cure of which prolonged drainage of the biliary tract was indicated. Archibald and Flexner demonstrated that bile mixed with gallbladder mucus produced no changes in the pancreatic cells, whereas bile unmixed with the same mucus produced destructive changes. Blockage of the cystic duct by stone, adhesions or edema, or infected bile found in cholecystitis all prevent the apparently necessary admixture of liver bile and gallbladder mucus. Without wishing to enter into the age-long controversy between the champions of promiscuous cholecystectomies and the more conservative, perhaps more physiologically minded, advocates of selected cholecystectomies, we take the stand that a gallbladder capable of functioning, *i.e.*, excretion of mucus, concentration of bile in the passage of water and inorganic salts from the blood, should never be removed if the head of the pancreas is enlarged, hardened or edematous. We also believe that, in the presence of valid indications for cholecystectomy, *i.e.*, empyema, destruction of mucosa by infection, impaction of calculi or chronic

hydrops, choledochotomy should be resorted to in order to relieve the pancreatic dysfunction. In rare, selected cases, cholecystoduodenostomy might be indicated.

TABLE VI shows the length of time during which our patients have been checked up and the clinical results obtained.

TABLE VI

Number of years observed	Number of cases
10 years	4
7 years	3
5 years	6
4 years	4
3 years	2
2 years	6
12–18 months	3
Total	28

Clinical Results

	Per cent
Symptomatically cured	60
Improved	20
Unimproved (noncooperative patients)	14
Surgical deaths	6
Diabetic	1
Asthenia	1

By prolonged drainage we mean that a rubber drain should remain in the gallbladder or cystic duct for 10 to 14 days and that the fistula should be kept patulous for four to six weeks longer. Drainage may even have to be prolonged for months in very chronic cases. It goes without saying that these patients should so modify their *modus vivendi* as to obviate a recurrence of the biliary tract stasis which was the original cause of their trouble. We feel that this postoperative check up is just as important in chronic pancreatitis as in gastric or duodenal ulcer.

CONCLUSIONS

(1) Thirty cases of chronic pancreatitis are analysed, illustrating the extreme difficulty of making a positive preoperative diagnosis.

(2) The close interrelationship of the biliary tract and pancreas is reemphasized.

(3) Operative recognition of chronic pancreatitis is probably often missed.

(4) Cholecystostomy, choledochotomy and, rarely, cholecystoduodenostomy offer the only surgical means of draining the pancreas through its duct or ducts.

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THE SUPERIOR LARYNGEAL NERVE AND THE SUPERIOR POLE IN THYROIDECTOMIES *

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FROM THE THYROID CLINIC OF THE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

WE HAVE reached an impasse in the treatment of thyrotoxicosis by accepted agencies, medicinal, the roentgen ray, surgery. We know the limitations of some, the wide field and usefulness of others. There is no doubt that in course of time a new remedy will be forthcoming, a specific, an organic compound which will provide the economy with what it needs and arrest this hyperplastic process. We have already seen what a profound influence iodine or the iodides have over this process; how in the space of a week or ten days the clinical and pathologic aspects will be so profoundly affected; the metabolic and pulse rate cut in half, the nervousness gone, the proliferated cells in the acini replaced with colloid, the patient half well. Soon, I believe this new remedy will be found, and, supplementing iodine, complete the cure.

Until then we must be content with other agencies and of these surgery gives eminent satisfaction. We acknowledge relapses in 3 per cent., but all in all there are no patients more grateful than the thyrotoxic subjects who have been relieved by surgical procedures.

The hazards of the operation have been reduced from year to year. The profession must not be alarmed by the misstatements that creep into the literature. I have in mind especially the statement of one radiologist who announces an operative mortality rate of from 0 to 20 per cent. and one nondescript writer who charges surgical therapy with recurrence in over 20 per cent. These statements of course are preposterous. As a matter of fact, in the well organized clinic, depending upon the nature of the material, the mortality for toxic goitre ranges from 1 to 3 per cent. It so happened that last year (1932) in this thyroid clinic the mortality rate was zero. There were no fatalities. For this splendid record there are many explanations. But having deduced operative hazards to a minimum, we have turned our attention to the elimination of postoperative discomforts.

There is no question but that in the past after a thyroidectomy many patients were very uncomfortable from accumulations of mucus in the trachea, frequent short coughs, efforts at expectoration which are painful, pain on swallowing or various reflex pains (thyromandibular and vagopinna). If we can prevent or minimize them we are making a real contribution in this particular surgical field.

* Read before the Philadelphia Academy of Surgery, October 2, 1933.

In the past, in the performance of a thyroidectomy, the surgeon's mind has been focused on two structures, and these he has been warned to avoid, the parathyroid glandules and the recurrent laryngeal nerve. That there is such a structure as a superior laryngeal nerve is scarcely mentioned. We were so impressed with a description of the anatomy and function of this nerve by Roeder (Archives of Surgery, vol 24, No. 3, March, 1932) that for the past year we have paid as much attention to the superior as to the inferior or recurrent laryngeal nerves.

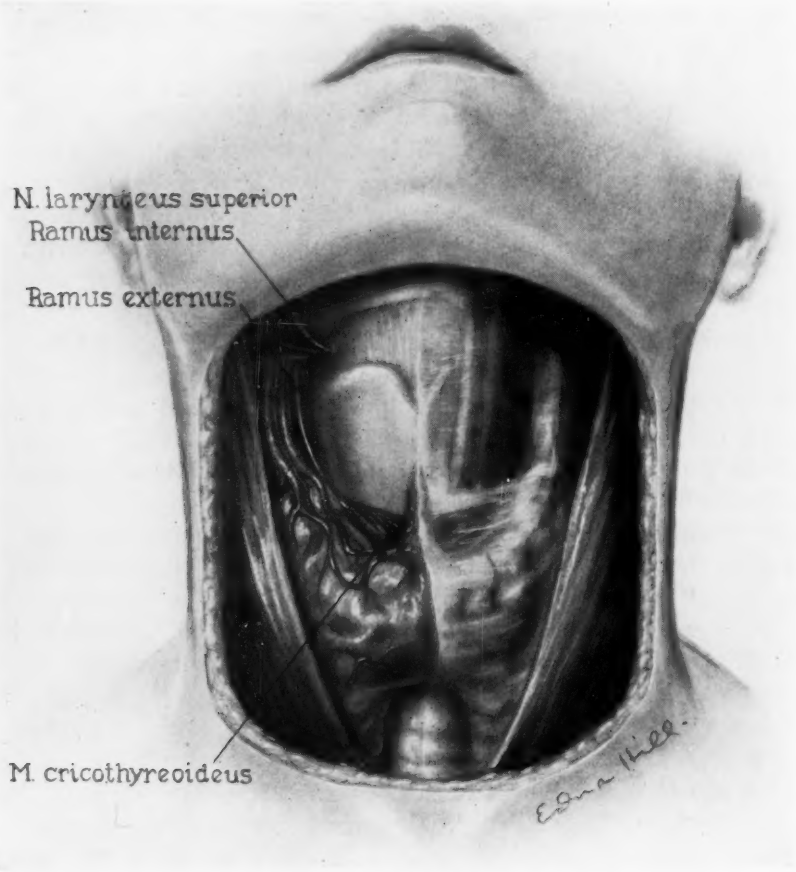

FIG. 1.—Diagrammatic sketch showing anatomic relations.

The superior laryngeal nerve supplies the interarytenoid muscles, which are adductors of the posterior ends of the vocal cords. Thus, if both superior laryngeal nerves are damaged, there may be partial loss of voice. Furthermore, with injury to these nerves there may be loss of sphincteric action of the upper portion of the larynx; thus, fluids may enter the air passages and induce an inspiration pneumonia.

As Roeder says, the normal sensory nerve supply to the mucous mem-

brane of the upper half of the larynx is an extremely important protective mechanism, producing, when irritated, a sphincteric action of the larynx above the vocal cords through contractions of the interarytenoid, the thyro-arytenoid and the lateral crico-arytenoid muscles, which are supplied by the superior as well as by the inferior laryngeal nerves.

As being related to the superior laryngeal nerve these two complications are merely referred to in passing. Our primary purpose is to discuss discomforts and of these, first, the accumulation of mucus at the entrance to the trachea.

For many years, Doctor Frazier speculated as to the cause of this: at first he charged it to baring of the trachea as the isthmus was removed; then to incidental trauma to the trachea; then to edema of the trachea; then to some disturbance of its vasomotor supply; these were pure hypotheses. A much more reasonable theory, one with a reasonable anatomic explanation is that injury to the superior laryngeal nerves causes anesthesia of the larynx and the region of the epiglottis. Loss of sensation here abolishes the cough reflex, hence mucus accumulates. Since we have treated with much consideration and respect the superior laryngeal nerve, there has been the most gratifying relief.

Secondly, the troublesome little abortive cough or "hacking" was an ineffective attempt on the part of the patients to rid themselves of the accumulated mucus, and since these accumulations are now under control, the coughs have disappeared.

A third discomfort is pain on swallowing. The act of swallowing brings into play the constrictor muscles of the pharynx and of these the inferior constrictor is the only one exposed during a thyroidectomy, and it should be protected from injury as much as possible. In the act of swallowing, the muscles which elevate and depress the hyoid bone are brought into play directly or indirectly. These include among others the thyrohyoid and sternohyoid muscles and if the latter on one side or the other were bisected, the patient would experience some discomfort.

Among the discomforts are included certain referred or reflex pains. One of them is referred to the lower jaw, and usually to a molar tooth. In the earlier contributions from this clinic attention was called to this referred pain on ligation of the superior thyroid artery under local anesthesia. During the past year a certain number of patients complained of pain experienced in the region of the lower jaw. Without a reasonable explanation at the time, little attention was paid to their complaints. Roeder (*loc. cit.*) calls this pain the thyromandibular reflex and traces its origin from the sympathetic fibres in the superior thyroid artery to the superior cervical sympathetic ganglion, thence to the first or second posterior cervical root ganglion by way of the gray rami communicantes, and from there to the posterior horn of the spinal cord where it sends its impulses into the origin of the spinal root of the trigeminal nerve. Obviously the superior thyroid artery must be ligated in the course of a lobectomy so that there is no way of avoiding this minor dis-

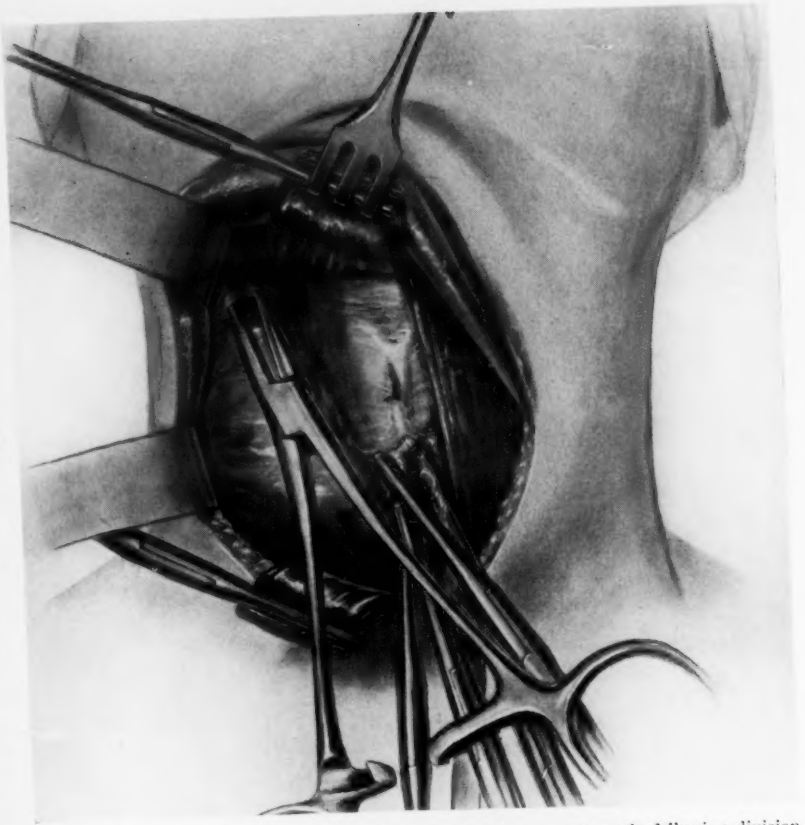

FIG. 2.—Drawing showing splitting of fascia surrounding superior pole following division of isthmus.

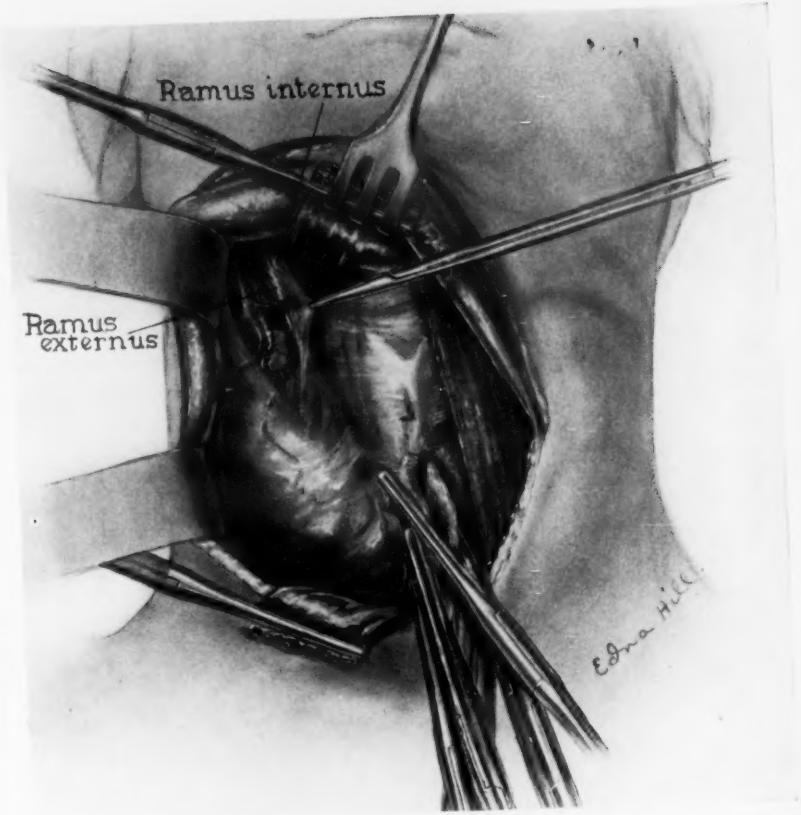

FIG. 3.—Diagram showing superior laryngeal nerves saved by division of the fascia and exposure of superior thyroid vessels.

comfort. Roeder also calls attention to a pain referred to the external rim of the external auditory canal and to the lower internal portion of the pinna, what he calls the "vagopinna reflex" but with this we have no experience. The pathway of this reflex pain is from the superior laryngeal nerve to the ganglion of the trunk of the vagus, thence to Arnold's nerve, with its sensory distribution to the ear.

If it be true that the superior laryngeal nerve plays so important a part as a factor in postoperative complications and discomforts, obviously every step should be taken to protect it. At one time it was our routine technic in some cases to pass an aneurysm needle behind the pole for isolation, in others to burrow under with a hemostat. The whole pole (vessels, lymphatics and fascial covering) was grasped with two Kocher hemostats, bisected and the central stump ligated. By this method not only was the external branch of the superior laryngeal nerve included in the ligature, but the accompanying traction on the pole in course of isolation of necessity damaged either temporarily or permanently the internal branch.

How can one ligate the vessels of the superior pole and not injure the superior laryngeal nerve, either its external or internal branch? This can be accomplished if one avoids traction or rough manipulation of the pole itself or the structures to the inner side of it, and with adequate exposure dissect the superficial flap of skin and platysma at least to the upper level of thyroid cartilage, and then bisect the ribbon muscles on one side or the other, with wide retraction of the wound edges. When the pole is clearly in view, Doctor Frazier divides this reflection of the pretracheal fascia, either by blunt or sharp dissection (Figs. 1, 2 and 3). In the trough between these two walls of fascia lie the superior thyroid artery and vein and these may be tied either together or separately. Thus, both branches of the superior laryngeal nerve escape injury.

SURGICAL TREATMENT OF TOXIC GOITER *

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THIS paper is a review of a series of patients operated upon by the writer for toxic goiter at St. Luke's Hospital during the past seven years. It includes private patients, although the great majority have been under the general care of the Thyroid Clinic of which Dr. George M. Goodwin is the chief.

In the first portion of the paper I propose to touch upon some of the contributions of New York physicians and especially members of the New York Surgical Society to the surgical treatment of goiter, particularly the toxic group, then to discuss the operation and finally the results obtained.

Doctor Halsted[1] stated that up to 1887 there had been but 30 goiter operations performed in America. The first operation was done by Dr. Charles Harris of New York in 1807, with recovery of the patient, and the second by Dr. Valentine Mott, whose patient succumbed.

The first and second cases of thyroid operations presented before the New York Surgical Society were by Dr. Arpad Gerster[2] in 1882 and 1884. In 1889, ten years after the founding of the Society, Dr. Frank Hartley[3] read the first paper on thyroid surgery, "Operations upon Struma." None of the cases described was toxic.

It was not until five years later that a case of exophthalmic goiter was shown. The reporter was Dr. Charles K. Bridden.[4] The patient had been treated with increasing doses of potassium iodide. Doctor Bridden observed that the effect on the goiter had been marked but that the eyes were as prominent as before.

Doctor Kammerer in the discussion said that he had operated on two cases of exophthalmic goiter some years before, one by ligation of the four arteries, the other by resection. Both had died apparently of thyroid crises. These were the only cases he had lost out of a considerable number of thyroid extirpations.

In the following year, 1895, Dr. W. B. Coley[5] was the first to show a patient who had been operated on for exophthalmic goiter. The operation consisted in removing the entire left half of the gland and closing the wound without drainage. It was noted that hemorrhage was difficult to control. The wound healed by primary union.

Two important contributions by members of the New York Surgical Society, although not presented before the Society, appeared in 1904 and 1905. Dr. B. F. Curtis[6] in an article entitled "Thyroidectomy and Sympathectomy for Exophthalmic Goiter" reported his experience. He had resected one lobe in 11 cases, with three deaths. Of the survivors six were cured, one improved and one lost sight of. Because of fear of postoperative crises

* Read before the New York Surgical Society, December 12, 1934.

he had done cervical sympathectomy on seven patients, in all but one of them bilateral. Two of these patients died from acute hyperthyroidism and a third fatality was probably due to the anesthetic. Of the survivors three cases were cured and one improved.

The second of these papers by Dr. Frank Hartley[7] was entitled "Thyroidectomy and Exophthalmic Goiter." In a period of about seven years he had operated on 15 cases with only one death. The 14 survivors seen at periods varying from one month to seven years were in good health and able to work. The reason for the good results he believed to be due to the removal of sufficient diseased gland and where this could not be done the production of atrophy in the gland which was left, presumably by ligation of the arteries. Usually he found the removal of one lobe and the isthmus sufficient but at times removed some of the opposite lobe as well. He had found rest in bed and medicinal treatment for two or three weeks prior to operation of great benefit. This paper appearing in 1905 seems to me to be remarkable for keenness of judgment and results obtained.

Dr. John Rogers[8] who has made many contributions to the treatment of thyroid disease reported in 1914 a series of 208 cases treated by ligation of one or more vessels. There were four operative deaths. About half the cases required subsequent treatment. Of 36 who had had quadruple ligations at least a year before, 25 considered themselves well and two had died of extraneous causes. The nine remaining were unable to do ordinary work.

In 1920, Dr. Charles H. Frazier[9] of Philadelphia read a paper before a joint meeting of the Philadelphia Academy of Surgery and the New York Surgical Society on the "Management of Toxic Goiter from the Surgical Point of View." He reported an operative mortality in the preceding five years of one and a fraction per cent. When it is recalled that preoperative preparation with iodine was not practiced until several years later this is a splendid showing.

In recent years Doctor Heyd[10] presented a paper on thyroid surgery including 95 cases of hyperthyroidism before the New York Surgical Society. Doctor Goetsch[11] gave to the Society an analysis of the mortality factors in his very large experience of 1,553 patients, including both toxic and nontoxic cases.

Other contributions from New York surgeons in the past ten years are those of Dowd[12] who reported 150 thyroid operations between 1899 and 1924, including all types of cases, Parsons'[13] study of 200 patients operated on for hyperthyroidism at the Medical Center and Pool and Garlock's[14] report of end-results of the surgical treatment of exophthalmic goiter at the New York Hospital. The studies of Kessel and Hyman[15, 16, 17] from the Mount Sinai Hospital on the spontaneous course of exophthalmic goiter are also of particular interest. Their final paper is an analysis of operative results.

Surgical Management.—This series numbers 154 patients of whom approximately four-fifths are listed as exophthalmic goiter and the remainder adenomatous goiter with hyperthyroidism. Seven had had previous surgery.

Women predominate in the ratio of seven to one. The ages varied at operation from 12 to 73 years. Eight of the group were colored, a proportion not far from that among general admissions to the hospital.

Preoperative Preparation.—In our Thyroid Clinic, operation has been advised as the treatment of choice to toxic patients. They are prepared with Lugol's solution and rest. In a few instances where the individual has already been on iodine therapy and has become iodine fast we have been able to secure a remission, after a month's rest from the drug, and then proceed successfully with the operation.

Anesthesia.—Avertin with gas and oxygen has been for some time the routine anesthesia. It has proved very satisfactory in this group of excitable patients.

Operation.—The operative procedure consists in subtotal resection of both lobes with removal of the isthmus and pyramidal lobe if present. In a number of the cases of toxic adenoma, however, where the disease was confined to one lobe and the other appeared normal in size and consistency, it has been left. In the course of the series I shifted from catgut to silk and also cut down the number of wounds drained. Whether due to the silk, absence of drain or increased care and experience on the part of the operator, there has been a great improvement in the wounds. Formerly they continued to collect and discharge serum for a week or more in over half the cases, whereas they now remain closed without incident in 80 per cent. I believe that the less irritating ligature material is a factor in this improvement.

Amount of Gland Left.—I have tried to estimate the amount of thyroid remnant in many of the patients and find it has averaged about a third of a normal gland. The amount left should of course vary in the individual case depending on the intensity of the toxemia, size and character of the gland and age of the patient.

Approximately 10 per cent of the patients have been operated upon in two stages, although in none of them has a ligation been done. Resecting a lobe at a time in the more severe cases is a safeguard to the patient. Sometimes the two-stage operation is planned ahead of time, more often the decision has been reached on the operating table, depending on the patient's condition, the technical difficulties, and time consumed in the resection of the first lobe. Control of bleeding and care in handling tissues seem to me of more importance than speed. I have tried doing the second stage as early as two days and as late as six weeks after the first, but prefer as a rule about one week's interval. This gives time for the postoperative reaction to subside and at the same time is early enough for the flaps to separate easily.

Postoperative Care.—On return to the ward the patient receives a retention enema of tapwater with Lugol's solution. Iodine was at first administered for two months but now we give it for a week only and the patients do just as well. Sedatives are administered freely.

Two cases in this series have had secondary hemorrhages sufficiently severe to require reopening the wound, one on the first and the other on the second day postoperative. In both, silk ligatures had been used. In nine patients

whose cardiac rhythm was regular before operation temporary fibrillation occurred postoperatively.

Mortality.—There was one death, a mortality under 1 per cent. It is of interest that this occurred in the only patient in the series who was not adequately prepared with iodine. She was not thought to be very toxic and had a basal metabolism of only +23. Warning factors, however, were age 59 years and a five-year history. Death occurred in 48 hours from a hyperthyroid crisis.

LATE RESULTS.—We have had information of about 90 per cent of this series at some time since their discharge from the hospital. There has been, as far as we know, but one death. In this case the woman who had been doing well, according to reports, developed erysipelas which proved fatal.

For the purposes of this follow up study I have taken the 100 cases in whom we have had the longest periods of observation, varying from six months to six years, including only those on whom there are metabolism tests as well as clinical examinations. The average period for the group is two and one-quarter years, and the average number of metabolism tests between four and five.

Eight of them have had a continuation and six a recurrence of hyperthyroidism, 14 in all in whom operation has failed to accomplish prompt and continued relief. The remaining 86 have been relieved as far as we have followed them, although in two of these metabolism tests of +37 and +31 have raised the question of relapse despite lack of clinical evidence.

Treatment of Continuation and Recurrence.—None of these cases has been reoperated on. Six of them have had radiotherapy and in the five in whom we have been able to carry this through the outcome has been good. It is our impression that postoperative cases have responded to roentgen ray more quickly and satisfactorily than the unoperated patients with Graves' disease. Three are well on iodine medication. Three more consider themselves well and have not found it worth while to take any treatment. Of the remaining two, one was treated elsewhere and was working and reasonably well when last examined by us two years postoperative. The other developed marked regeneration of her gland, loss of weight and a metabolism of +17 five years after operation. She refused further treatment.

Hypothyroidism.—None of the patients has myxedema. Six have had postoperative metabolic tests below —20. One of these was kept on thyroid medication for five months and another for two.

Metabolism.—The basal metabolism is of great importance in the diagnosis of hyperthyroidism and in following the progress of the treated patients, but like all laboratory tests it is not infallible and must be judged in connection with the clinical findings. For practical purposes we consider readings of up to +20 as within the normal range.

The average of the last tests on this series is ±0. Nineteen of the 100 have had one or more basal tests over +20. Twelve of these 19 were in patients whom we considered as having recurrence or continuation. In the remaining seven there has not been clinical evidence of hyperthyroidism.

On the other hand in two recurrent cases the highest tests have been +14 and +17 (TABLE I).

Weight.—The average gain in weight in this series for the period of observation is 18 pounds and only 12 of the number are below their preoperative weight. On the other hand the fear of undue gain would seem to be unfounded as in those patients in whom we have this information the postoperative gain averaged only one pound more than the previous weight loss. In nearly one-half the patients the weight reaches a peak and then recedes somewhat. A number of those who made large gains were women about the age of the menopause. Curiously enough in a few patients who had been gaining weight during their illness there was loss after operation.

TABLE I

Composite Basal Metabolism Tests on 100 Patients with Toxic Goiter Followed from Six Months to Six Years after Operation

Admission or highest metabolism	99	patients	averaged	+52
Preoperative after iodine	97	"	"	+22
Postoperative before leaving hospital	93	"	"	± 0
Three months postoperative	64	"	"	+ 1
Six months	81	"	"	+ 1
One year	78	"	"	+ 1
Two years	48	"	"	+ 1
Three years	25	"	"	± 0
Four years and over	20	"	"	± 0

Pulse.—In a good many patients lability of the pulse remains although it is usually normal under basal conditions. In only eight of the series was the last basal pulse-rate 90 or more.

Nervousness.—Hyperthyroidism often develops in an individual with an unstable nervous make-up and its relief is not going to change the natural constitution. I can think of individuals in the series who are full of nervous symptoms and yet maintain gain in weight and normal metabolic rates. For the group as a whole there is an emotional and nervousness irritability which is greater than that of average individuals.

Exophthalmos.—Most writers report improvement of the exophthalmos in a majority of the patients operated upon. Kessel and Hyman,[17] however, in their study of the results of operations, made exophthalmometer readings and did not find a general improvement.

In my experience impressions are likely to vary and are unreliable. As far as this series goes as many patients are reported as unimproved or doubtful, as improved or free of their exophthalmos. The prognosis concerning this feature is very doubtful, particularly if the exophthalmos is marked. One of our patients in whom exophthalmos was not present during the illness began to show a little three years after operation although the basal metabolism remained normal.

No attempt has been made in this study to consider the cases of Graves' disease separately from those of toxic adenomata as the series is too small. It is my impression, however, that the latter form the more satisfactory group.

Condition of the Patients as Last Seen.—Ninety-five are relieved of their hyperthyroidism, including three on iodine medication and two whose last basal tests were high in the absence of clinical symptoms of recurrence. Three with mild continuations consider themselves well and do not feel that they need treatment. Of the remaining two, one was improving under roentgen ray treatment for continuation of the disease when she left town and the other has a recurrence five years after operation.

SUMMARY.—The surgical treatment of toxic goiter gives, on the whole, good results.

The mortality is under 1 per cent in the series reviewed.

Fourteen per cent have had continuation or recurrence of the disease.

Roentgen ray therapy has proved a useful method of treatment in such cases.

The result at last examination in 100 cases followed six months to six years has been 98 per cent good or fair.

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Discussion.—Dr. William Barclay Parsons (New York) wished to speak first of the question of technic. He was very glad to learn that silk was being used. Dr. Frank Meleney stimulated him to the use of silk several years ago and he had established apparently a base line for excessive exudations and infections. For a period of several years they had had some 40 per cent excessive exudation with about 14 per cent infection. After using silk, draining wounds have been cut down to 9 per cent and infections to 1.6 per cent. About two years ago, some linen was brought out which was very nice from the standpoint of handling. The caliber of this linen, however, was distinctly larger than the finest silk we had been using and we immediately began having trouble with our wounds, demonstrating well that the points Doctor Halsted brought out many years ago were sound; one of these was stress upon the fineness of the material. If you never break your silk, the chances are it is not quite fine enough.

In regard to stage procedures, his feeling has been that where the second stage is done within a comparatively few days of the first, you are dealing with what might be called fresh reparative tissue, and it is better to use absorbable rather than nonabsorbable material for the second stage because infection would be a little more severe than after the first stage.

The question of recurrences and continuation of symptoms is interesting. We have felt that the majority of cases that seem to be recurrences are in reality continuous or persistent hyperthyroidism; in other words, a failure of immediate cure. Our experience has been the same as Doctor Smith's, that radiotherapy is a very useful agent in controlling these cases. Some of our thyroid group have been very much interested in radiotherapy and have followed quite a number of cases over a period of years. It seems that the small glands with mild symptoms represent, practically speaking, the only type of case that will give a reasonably high success with its use. Leaving out of discussion whether or not one believes in radiotherapy as a standard method of treatment, it will help control the continuing cases because they have been changed into cases with small glands and with mild symptoms.

We have attempted to attack some of the nervous manifestations associated with hyperthyroidism by having a psychiatrist attached to the thyroid clinic in the Presbyterian Hospital. To attempt any formal psychiatry while the individual is still suffering from an organic pathologic condition is futile. However, after the organic disease has been controlled, whatever constitutional, physical disturbances may be present may be helped very materially by proper and careful psychiatric attention.

Dr. Emil Goetsch (Brooklyn) said that there were a few points upon which one might enlarge, for instance, the iodine-fast goiter patient, and in this connection he wished to refer for a moment to the use of iodine in the medical treatment of the hyperplastic thyroid by citing the recommendation of Kocher, made about 1883—a recommendation which is just as valuable today—namely, that no case of goiter showing symptoms of hyperthyroidism should be treated with iodine. Trousseau was the first to point out that, in spite of the transient improvement produced by iodine, there is a subsequent relapse into a more toxic hyperthyroidism as a result of such treatment. He felt that the misdirected treatment with iodine in the hope of benefiting patients with hyperthyroidism was so widespread that it was hardly short of a crime and is comparable in its misdirection to the former treatment of ovariectomy for hysteria. Further, he believed that more harm has been done by the misuse of iodine in hyperthyroidism, for there are so many more patients with goiter than there were with hysteria. These remarks are of course referable

to the indiscriminate treatment of goiter with iodine and are not applicable to the use of iodine for the first time preoperatively in the preparation of the hyperplastic thyroid for operation.

We know that when iodine is given to the patient with hyperplastic goiter, the thyroid gland rapidly stores the iodine, undergoes colloid involution and in a period of a week to ten days there is a remarkable clinical remission in the disease. In fact, hyperthyroid patients in preparation for operation frequently become so well in this remission that they may even believe that the operation of thyroidectomy is unnecessary. On the other hand, if iodine is given and operation is not carried out, there is a relapse in the course of six weeks to two or three months and the resultant acute hyperthyroidism is at times nothing short of terrifying. He had seen patients in this state in which the pulse was over 220, almost uncountable. The tremor and agitation were most marked and the mental state practically maniacal. In fact, he had seen a maniacal outburst directly subsequent to a prolonged period of iodine treatment in a case of a simple, mild hyperplasia of the thyroid. The unfortunate fact is that in this state of hyperthyroidism caused by iodine, the further giving of iodine, no matter in what doses, produces little or no benefit at all. In such instances prolonged periods of rest with sedatives is necessary and in the end-stage operations are required. A study of their mortality statistics has brought out the fact that the goiter patient who has received indiscriminate treatment with iodine immediately becomes a more dangerous operative risk. On the other hand, he might say that they have had no death from postoperative hyperthyroidism in any operative case of goiter in which iodine treatment had not been previously carried out. This is a forceful argument for the restriction of iodine treatment to the immediate preoperative period. The metabolism in the case of the indiscriminately iodized patient is not a safe guide to operability, for they have found that many iodized patients with a metabolic rate of not exceeding plus 35, and thus thought to be within safe range for operation, have had rather toxic postoperative reactions and have in a few instances died in postoperative crisis. It would seem that the indiscriminate use of iodine has obscured the value of the metabolism in estimating the true toxicity of the patient.

A word may be said regarding the treatment of the iodized patient showing symptoms of exacerbation. The question is one of stage operations oftentimes or of waiting until the thyroid gland again becomes sensitive to further treatment with iodine. Patients will often choose to wait almost indefinitely rather than submit to stage operations. Sedative treatment is carried out for two to three months or even longer before iodine will again cause a remission and thus allow a double lobectomy to be performed. He has waited as long as nine months. It is surprising to see how long the clinical exacerbation of hyperthyroidism will persist after the patient with hyperthyroidism is treated with iodine.

He has never practiced the routine administration of iodine following thyroidectomy. It has been widely taught that such procedure tends to prevent recurrence of hyperthyroidism. He has not been able to understand the rationale of this treatment and might say further that recurrences in his experience have been no more frequent than those reported after the practice of giving iodine postoperatively. Once the thyroid gland has become iodine-fast, there is no virtue in giving more iodine. The residual stumps of thyroid gland after thyroidectomy have undergone all the involution of which they are capable following the preoperative iodine treatment. The sooner the thyroid gland is relieved of the influence of a drug as potent as iodine, the sooner

normal function is restored. The mortality following thyroidectomy is not related in his opinion to the administration of iodine following operation.

He was pleased to note that Doctor Smith finds the use of silk such an advantage. Having been brought up in the clinic of Doctor Halsted, he was introduced to this technic early in his experience, and is convinced of its advantages.

Doctor Smith referred to the use of stage operations in certain instances. It is well to emphasize this point for unless this practice is followed in the highly toxic cases and particularly in those which have received indiscriminate treatment with iodine, an increase in the mortality rate is apt to follow. A patient comes to mind who several years ago was *in extremis*, comatose and moribund, upon whom he performed five operations in stages. She had a huge exophthalmic goiter. She finally recovered completely and is well and at work today.

Reference may be made to the extent of resection of the thyroid gland and to the possibilities of postoperative hypothyroidism. Soon after the general use of iodine in the preoperative treatment of exophthalmic goiter, it was noted that the thyroid gland became larger, more firm, less vascular and showed a marked colloid accumulation in the glandular acini which were greatly distended. Thereupon when the resection was performed leaving a residual stump on each side of the same gross amount as had been previously practiced before the use of iodine, it was found that postoperative hyperthyroidism not infrequently resulted. This was a natural sequence for the residual stumps were in large part composed of inert colloid and a minimum of thyroid parenchyma with the result that there remained after thyroidectomy insufficient physiologically active thyroid tissue to preserve normal metabolism. The greater the colloid reaction in the gland, the larger residue one must leave, or vice versa; in a fleshy-looking, vascular gland with a diminished colloid reaction the resection must be more extensive.

TRAUMATIC INTRATHORACIC RUPTURE OF THE THORACIC DUCT WITH CHYLOTHORAX

REPORT OF A CASE WITH RECOVERY

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TRAUMATIC chylothorax is an unusually interesting, though rare, complication of traumatism or wounds of the thoracic duct. It is not mentioned in most of the medical classics.

The history of this condition dates back to the seventeenth century (Bartolet, 1633; Diemerboeck, 1685; Hoffman and Bonet) but accounts of the cases then reported are too vague and incomplete to be acceptable. It is interesting to note that no case was reported during the Civil War by military surgeons.[1] The first authentic case was reported by Quincke[2] in 1875. From then until 1912, when Zesas[3] reviewed the literature, only eighteen cases were on record. In 1928, Lenormant's[4] review added eight cases. From 1928 until 1932, only seven additional cases were noted by Macnab and Scarlett,[5] which, in addition to their own, brought the total to thirty-four. Mouchet's[6] review in 1933 revealed forty-three cases. Heppner[23] reported a case of bilateral chylothorax and chyloperitoneum of traumatic origin in 1934, and Scott[25] a case of traumatic chylothorax in the same year.

The present case appears to be the forty-sixth on record, of chylothorax of traumatic origin, the sixth in the North American continent, and the second to recover in the latter group; those of Watts,[7] Andrews,[8] Macnab and Scarlett,[5] and Heppner[23] failing to survive, while Scott's[25] case recovered.

The total number of cases of chylothorax, from any cause, was found in 1931 by VanNuys[9] to be sixty-six. Since then, as far as can be determined, fourteen cases have been added, bringing the total to eighty.

ETIOLOGY.—Chylous effusion into the pleural cavity is the result of a break in the continuity of the thoracic duct, from direct or indirect trauma, or from pathologic processes which obstruct or partly destroy the duct.

Traumatic rupture may be due to operative, self-inflicted knife or gunshot wounds in the neck or thorax; it may be the result of external violence causing fractured vertebrae or ribs, which tear the duct, or it may be due to closed trauma where no fractures or wounds are present and where the rupture, in the opinion of Lenormant, is the result of bursting, since the intra-duct pressure is normally high, particularly after a heavy meal, and compression of the thorax, during an injury, produces a pressure too great for the duct wall to withstand. Hyperextension of the spine during an accident, with excessive stretching of the duct leading to rupture has been suggested as a possible cause.

The morbid anatomic causes of chylothorax in the cases reported include malignant metastases of various types of tumors, thrombosis of the left sub-

clavian vein, tuberculosis, chiefly tuberculous glands, Hodgkin's disease, aneurysm of the duct, perilymphangitis, cirrhosis of the liver, and filaria. An intrinsic new growth or inflammation of the duct itself must also be considered as a cause of rupture.

Anatomy and Physiology.—The thoracic duct, elastic and about two or three mm. in diameter, conducts the chyle from the receptaculum chyli which lies anterior to the body of the second lumbar vertebra, to the left internal jugular vein at its junction with the subclavian. It passes from the abdomen through the aortic opening of the diaphragm, lying in the loose tissue between the vena azygos major and the aorta, and ascends with a gradual sinistral inclination that brings it posterior to the aortic arch and esophagus opposite the body of the fourth thoracic vertebra, whence it continues upward in the superior mediastinum to the left of the esophagus. During its ascent, it may divide into several branches which usually reunite before its termination in the internal jugular vein, although it occasionally has been noted to empty through two or more orifices. It leaves the thorax to the left of the esophagus opposite one of the last two cervical vertebrae then bends laterally and forward, and then downward to the pleural apex, thereby reaching its destination. Its arch is higher than the subclavian artery. Its entrance into the vein is guarded by a double valve.

It has been noted in a few instances that the thoracic duct may anastomose with the right lymphatic duct and the azygos veins, and perhaps the percentage of such anatomic anomalies may be greater than is supposed, since in many cases of ligation of the thoracic duct in operations in the neck, no ill effects develop. In fact, Warschauer[11] has even suggested the advisability of intentional ligation of the duct in all operations in the neck where it might be endangered. Watts feels that the absence of chylothorax, following ligation of the duct in the neck and its occurrence in certain lesions of the duct, might be explained on the ground that in the latter conditions, the collaterals are often involved.

The function of the thoracic duct is to transfer the products of fat digestion from the intestines to the blood stream, in the form of chyle. The mechanism of fat digestion, its absorption into the lacteals and thence to the receptaculum chyli, is adequately described in any standard text on physiology. It is important to note, however, that not all the fat is absorbed into the lacteals since experiments have shown that some of it must be absorbed directly by the blood vessels of the villi, and carried to the liver by way of the portal vein, where it can be demonstrated in liver cells during absorption (Howell).[12] Furthermore, the amount of fat that may be absorbed from the intestine varies with the nature of the fat. The fluid fats, such as olive oil, are absorbed more completely, that is, less is lost in the feces than are the more solid fats such as mutton fat, spermaceti and pork fat.

Traumatic chylothorax occurs more than twice as frequently on the right side. In Lenormant's review of a series of twenty-four cases, the right side was involved in thirteen cases, the left in six, and both sides in five. In Macnab

and Scarlett's review of twenty-eight cases, fifteen were on the right, six on the left, and five on both sides. Mouchet reports twenty-one on the right, seven on the left, and four bilateral. The reason for this occurrence is based by Watts on an anatomic consideration, namely the close approximation of the right pleura and the duct, so that the forces that affect the duct are apt to injure both structures at the same time. This seems to be borne out by the case of Macnab and Scarlett.

On the other hand, some authors, especially Hammesfahr,[13] think that as a result of the negative pressure in the chest, chyle can escape into the pleura from the mediastinum through the normal intercellular spaces between the endothelial cells—Watts' case illustrates this view, since there was no tear in the pleura. According to J. L. Yates,[24] there are no intercellular spaces in this region, and a perforation of the pleura is always present, although frequently not recognized.

Grimault explains the predominance of right-sided chylothorax by the existence of more lateral collectors for the duct on the right side than on the left, since the hepatic collectors run above the diaphragm.

Clinical Features.—The three most striking clinical features of this condition are: the latent period before the onset of the symptoms; the rapid reaccumulation of the fluid within the chest after aspiration, and a gradual progressive emaciation which frequently ends in death.

In the cases so far reported, the average length of time which elapsed between the accident and the onset of symptoms was four days. In Macnab and Scarlett's case it was six days, and in the present case it was five days. The reason for the latent period is unexplained. The sudden, dramatic appearance of the symptoms is also characteristic; a patient having been uncomfortable only from the effects of the original accident and, apparently for no obvious reason, suddenly goes into shock, with dyspnea, a rapid, thready pulse, profuse, clammy perspiration and an abrupt drop in body temperature, often to 95° F. Physical examination at this time reveals the cardinal signs of fluid in the chest, usually with displacement of the mediastinum and heart to the opposite side. Aspiration of the chest, combined with a stimulant such as hot coffee or caffeine, parenterally, gives relief to the symptoms of shock, and the patient who, thirty minutes previously, appeared to be *in extremis*, will seem quite well. This picture of shock and its attendant findings is repeated every time the intrathoracic pressure becomes great enough to impair circulation and respiration by reaccumulation of the chylous fluid.

There has been some confusion in explaining the shock which occurs coincident with the effusion. Paitre suggests an anaphylactic basis for it; Macnab and Scarlett think that an abrupt disturbance of the pressure relations existing in the thoracic cavity, with partial compression of the lung, due to the sudden release into the pleural cavity, might explain it. In the present case, the amount of fluid in the chest, at least four liters, was enough mechanically to impair cardiac and respiratory efficiency and account for at least some of the shock, because it was noted on several occasions that, prior to aspiration of

the chest, the radial pulse was imperceptible, and during the process of aspiration, the volume of the pulse could be felt returning to normal.

The rapidity of reaccumulation of fluid after injuries to the thoracic duct is usually pronounced, and the amount of fluid large. Quincke aspirated twenty liters in ten days; Dietz, 27 liters in thirty-one days; Hahn, twenty-nine liters in three weeks; Macnab and Scarlett, thirty-five liters in forty-eight days; Grimault, twelve liters in six days. In our case, over fifty-two liters were removed in thirty-four days. However, in Paitre's[14] case, only 300 cc. were obtained altogether.

It has been noted in many instances that patients died of emaciation and asthenia, if they survived their original injury. The morbid physiology, although complex, accounts for this termination, or the near-termination, as in the present case, where the weight fell from 148 to 114 pounds in thirty days.

Of lesser importance as a clinical feature is the relative difficulty with which a definite diagnosis of chylothorax is made, and the number of times the chest is aspirated before one suspects chylous effusion. This is due to two things: the rarity of the condition, and the fact that the first few aspirations are usually blood-tinged to a greater or lesser extent. In the present case, the first two aspirations were so bloody that it was felt we were dealing with a hemothorax. In Watts' case, seventeen days elapsed, and the chest was aspirated six times before a diagnosis was made. Lindenberg[15] and Scott made the diagnosis on the first puncture. Most writers fail to state how many punctures were made before the diagnosis was established.

The Aspirated Fluid.—A thorough knowledge of the physical, chemical and microscopic properties of the fluid recovered from the chest is highly essential in the diagnosis and differential diagnosis of true chylothorax, particularly in those cases in which visible defect in the thoracic duct is not demonstrable at autopsy.

Milky fluid recovered from a chest cavity does not necessarily mean rupture of the thoracic duct. Bradbury,[16] in reviewing the classification of this type of fluid, mentions the early concept of three groups: chylous, the thoracic duct chyle; chyliform, in which the fat appears to be due to cell degeneration; the pseudochylous, in which the opacity is non-fatty. Because of the difficulty in differentiating the two varieties of fatty fluid, this classification has been more or less abandoned and, for simplicity, milky fluid is classified into two clearly defined types: chylous, any fluid admixed with chyle, and pseudochylous, in which the opacity may be due partly to emulsified fat, or to lecithin in some unexplained combination with globulin.

Wallis and Scholberg,[17] in a thorough review of the subject, have established certain "determining points," the salient features which differentiate chyle from pseudochyle; these include specific gravity, the microscopic fat, the rate of accumulation and the various qualitative and quantitative chemical tests.

Table I is a comparison between the fluid aspirated in the present case and the chylous and chyliform described by Wallis and Scholberg.

TABLE I

	Present Case	Chylous Fluids *		Pseudochylous Fluids	
		Wallis and Scholberg Determining Points		Wallis and Scholberg Determining Points	
Sp. gravity	1.100	0.017	Over 1.012	1.009	Under 1.012
Reaction	Alkaline	Alkaline		Alkaline	
Proteins	7.0%	3.95	3% or more	1.056	1 to 3%
Ser. albumin	1.0%	0.18	Most of albumin	0.56	
Fat	1.0%	1.58	0.4 to 4%	0.353	Low
Phosphorus	2.6 mg.				
N. P. N.	41. mg.				
Cholesterol	.166 mg.	0.26	Always present		Occasional
Glucose	.145 mg.	0.11		.071	
Salts	.581 mg.	0.818	As in chyle	0.747	As in lymph
Manner of collection	Very rapidly	Very rapidly	Very rapidly		Slowly and small amounts
Microscopic fat	Many globules Stain with Sudan III		Fine fat globules		Granules not fat
Cream layer	About 5–10%		Is usual		Not usual
Sediment	None		None		Usual
Color	Yellow-white		Yellowish-white		Pure white

(Present Case: .166 mg. / .145 mg. / .581 mg. in 100 cc. of fluid)

* From Bradbury, Nelson's Loose-Leaf Med.

Summarized, chylous fluid has a specific gravity of over 1.012; it resists putrefaction and does not coagulate; a "cream" layer forms on standing; there are many microscopic fat globules which are soluble in ether; the fat content is high, and the fluid accumulates rapidly. In contrast, pseudochylous fluids have a specific gravity under 1.012; there is usually no "cream" layer and no microscopic fat: the total fat content is low, under 0.4 per cent, and the fluid collects slowly.

In the present case there can be no doubt of its falling within the classification of true chyle; its chemical analysis is well within the range of that group, and its physical properties, chiefly the tremendous amount aspirated, leave no doubt as to its nature.

TREATMENT.—There is a marked diversity of opinion among writers with regard to a definite rule of therapeusis, indicating not only the difficulty, but the uncertainty as well, of attempting to set forth a routine form of treatment.

Surgical repair of the wound in the duct is sometimes possible in the neck, but is not successful in the thoracic portion, at the present time. When repair is impossible in the neck, ligation of the duct in that region is sometimes effective. When neither is possible, suture of a bit of muscle over the leak may seal it. Ligation in midthorax is almost certainly lethal. (Yates.)

Aspiration of the chest is usually a necessary procedure, but the frequency is a debatable question. If it is not done, the patient is threatened with suffo-

cation, and when the fluid is removed, the loss of chyle leads to inanition and death; consequently the majority of writers favor only the so called "emergency puncture" to relieve acute dyspnoea, with repetition as seldom as possible, because withdrawal of fluid creates a negative pressure within the chest which tends to increase the outpouring of fluid from the thoracic duct.

Others favor extensive thoracotomy or thoracoplasty for the sole purpose of producing positive pressure in the pleural cavity, thereby favoring the spontaneous closure of the duct. This has been done in approximately seven cases with four recoveries and three deaths. It was considered in the present case, but the idea was abandoned because of the disadvantage of possible infection, and it was felt that just as much good could be accomplished by more conservative treatment. As a matter of fact, it was noticed that, whereas thoracotomy would produce positive pressure, practically the same result could be obtained by replacing some of the aspirated fluid with air.

It would seem logical that, by modifying the diet to exclusion of all fats, the amount of chyle to pass through the thoracic duct should be diminished or stopped. In the present case a low fat diet had little, if any, effect, but when a totally fat free diet was instituted, the chylous effusion stopped in forty-eight hours. (This may, of course, have been coincidental.)

It has been suggested by Oeken[18] and Watts that introduction into the venous circulation of the aspirated chyle would tend to offset the emaciation attendant upon the loss of chyle. Oeken tried it, but his patient died. Watts was unable to try it because the chyle was infected, in his case.

Rectal feeding, exclusively, has been advocated by Hall and Morgan,[19] in order to secure absolute physiologic rest, absorption occurring by way of the colonic lymphatics and thence to the superficial lymph channels, to spare the lacteal system. Other writers discredit the idea, saying that it does not spare the thoracic duct, and clinical experience proves it without any particular value.

During the acute illness, it is highly essential to maintain the fluid and caloric balance of the patient. If this cannot be done with oral feedings, it must be done intravenously, or subcutaneously. Carbohydrates should be given in large amounts.

As Macnab and Scarlett[5] emphasized, the success of any form of treatment depends, in a large measure, upon the presence or the development of collateral lymph circulation. When the chyle is diverted from the thoracic duct, spontaneous recovery will take place.

Mortality.—The mortality in traumatic chylothorax is high. With the exception of Lindenberg,[15] who, as late as 1926, stated the mortality to be as low as 10 per cent., other reviewers of the subject are agreed that it is a little more than 50 per cent. Mouchet[6] reports 41 per cent of deaths in forty-three cases.

The prognosis depends on the complications, immediate and remote. Unless the fluid is removed before it causes too great cardiac and respiratory embarrassment, death will ensue. If the wound in the thoracic duct fails to

close, or if collateral lymphatic circulation fails to become established so that the chyle can reach the blood stream, death will occur from malnutrition and emaciation. If, during the course of thoracocentesis, infection is unwittingly carried into the chest cavity, the outlook is necessarily more grave.

It is also obvious that the nature and seriousness of the original accident would influence not only the prognosis but the mortality rate as well.

Case Report

A. C., aged forty-five, a railroad carpenter, was injured May 19, 1933. He fell from a scaffold twenty feet high, landed on his back among some large timbers, and was unconscious for about four hours. In the interim he was taken to the Summit Hospital at Oconomowoc, Wisconsin, where further examination, including roentgenograms, revealed a fracture of the olecranon process of the right ulna, a fracture of the right tenth and eleventh ribs about one and one-half inches from their articulation with the spine, and a

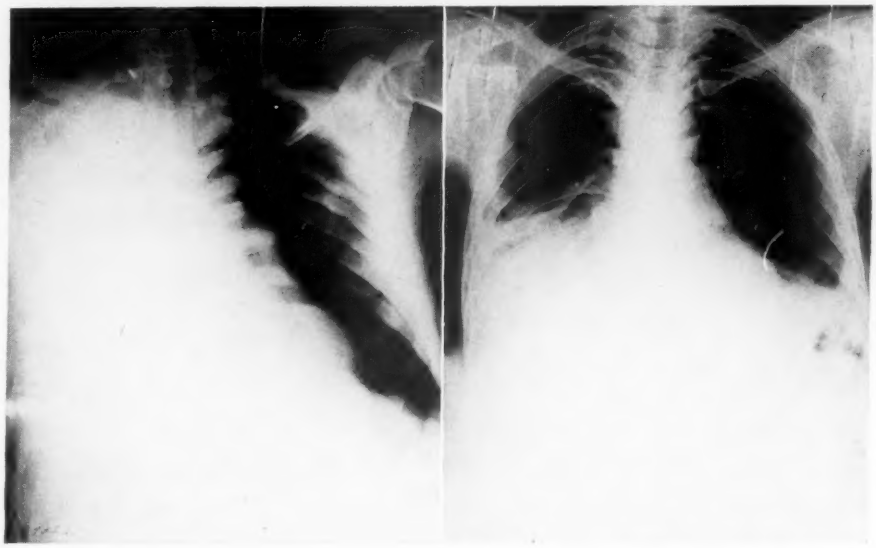

Fig. 1.—May 25, 1933, shows complete opacity of the entire right chest with displacement of the heart and mediastinum to the left and a large amount of pleural effusion.

Fig. 2.—June 28, 1933, shows a small amount of pleural effusion over the right lower lobe and in the interlobar space; the heart and mediastinum are drawn slightly to the right side.

fracture of the bodies of the eleventh and twelfth dorsal vertebrae. There was no fluid in the chest. In addition there was a severe concussion of the brain; stereoscopic skiagrams of the skull, taken six days later, revealed no fracture. He was given the usual supportive treatment, and his general condition improved sufficiently for him to be moved, on May 22, to the Milwaukee Hospital for further treatment.

At the time of his admittance to the Milwaukee Hospital, his physical examination was essentially negative except for a greatly edematous and discolored right elbow and hemorrhage in the soft tissue about both eyes. Temp., 98.8°; pulse, 96; resp., 20. The chest was resonant throughout and the breath sounds were normal. The urine was negative.

For the following two days the patient was quite comfortable, his temperature ranging between 98.6° F. and 99° F., his pulse between 70 and 90, and his respirations between 18 and 20.

On the fifth morning after the accident, May 25, the patient, rather suddenly, went into shock. The temperature dropped to 97° F.; the pulse rose to 130, became very weak and thready, and the respirations increased to 30, with marked dyspnea, but no cyanosis. Examination of the chest revealed all the signs of a large amount of fluid in the right pleural cavity, with displacement of the heart to the left. This was confirmed by a skiagram (Fig. 1). A diagnosis of hemothorax or pleurisy with effusion was made.

A needle was inserted between the eighth and ninth ribs in the post-axillary line and 450 cc. of bloody, turbid fluid was removed, giving prompt relief to the patient. The pulse, temperature, and respirations returned to normal.

The following morning, May 26, the patient again went into shock with the symptoms of the previous day, and two liters of the same bloody fluid were withdrawn, again giving the same dramatic relief to the patient. A blood examination revealed hemoglobin 75 per cent; R. B. C. 4,700,000; W. B. C. 12,500.

He continued to have relief for forty-eight hours, but on the 28th, the performance was repeated, and thoracentesis was again necessary, 1,020 cc. of fluid being withdrawn, the character of which, however, had changed from frank bloody to pink creamy fluid, and a diagnosis of chylothorax was made.

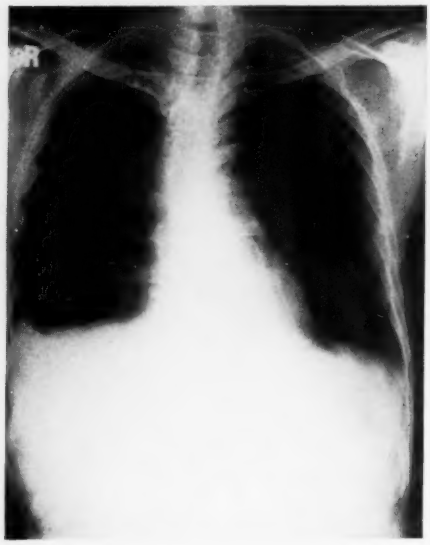

FIG. 3.—August 25, 1933, shows a normal chest except for very slight pleural thickening at the right base.

In another two days the process was repeated, and 3,000 cc. of fluid were withdrawn. In the meantime, the patient was placed in an oxygen tent several times during the day and night, which seemed to afford some relief from his dyspnea. His fluid and caloric balance were being maintained by intravenous injections of 10 per cent. glucose in normal saline solution.

From June 1 until June 24 it was necessary to aspirate the chest every day because of repetition of the shock syndrome to a greater or lesser extent. As much as 4½ liters were removed at one aspiration. By this time the fluid was entirely milky with a "cream layer" on standing, and chemically was definitely proven to be chyle. It also contained small masses of a fibrin-like substance which frequently clogged the aspirating needle. Daily cultures were sterile.

On June 20, an entirely fat-free diet was instituted, and by June 24, only 240 cc. were obtained with thoracentesis; 420 cc. on the 26th, and none on the 28th.

X-ray examination of the chest on the latter date, revealed only a small amount of fluid in the right lower chest with pleural thickening and diaphragmatic adhesions, and some fluid (coagulum?) in the space between the upper and middle lobes; the heart and mediastinum were now displaced into the right side (Fig. 2). On July 10, the blood cholesterol was 238 mgm., per 100 cc.

After June 28 no aspiration of the chest was necessary. Examination on July 21 revealed good resonance everywhere except over the right lower lobe, posteriorly, where there was some dullness, probably due chiefly to pleural thickening.

On July 29, sixty-two days after the accident, his condition improved enough to permit open reduction of the right olecranon process under local anesthesia. The widely separated fragments were joined with a mattress suture of kangaroo tendon, and his convalescence thereafter was normal.

After the onset of the chylothorax, the patient lost weight steadily, from 148 to 114 pounds, on July 5. Accumulation of intrathoracic fluid having ceased, a full diet including fats was begun, his weight immediately began to increase, and by August 25 it was 133 pounds. On that date he was discharged from the hospital in good condition, and an roentgen ray picture of the chest (Fig. 3) was virtually normal, with the exception of a few adhesions at the right costophrenic angle. On September 22, 1933, his weight was 138 pounds, and on November 8, 1933, it was 141 pounds.

Table II is a tabulation of the daily fluid intake, urine output, and amount of chyle aspirated from the onset of the chylothorax until the effusion ceased.

TABLE II

Date	Chest Fluid cc.	Total Intake cc.	Urine cc.	Date	Chest Fluid cc.	Total Intake cc.	Urine cc.
May 25.....	450	1,260	660	June 12.....	3,060	3,790	1,290
May 26.....	1,000	2,430	1,230	June 13.....	960	3,220	810
May 27.....		2,370	180	June 14.....	2,100	2,890	1,020
May 28.....	1,020	2,730	780	June 15.....	1,180	3,010	330
May 29.....		2,610	540	June 16.....	4,560	2,650	960
May 30.....	3,000	2,310	1,080	June 17.....	1,920	3,280	900
May 31.....		2,550	455	June 18.....	4,260	2,920	960
June 1.....	3,080	3,700	1,185	June 19.....	1,920	2,910	1,050
June 2.....	1,680	2,430	690	June 20.....	2,940	2,580	780
June 3.....		2,770	1,020	June 21.....	2,940	3,040	1,470
June 4.....	960	4,030	885	June 22.....	1,560	2,160	1,620
June 5.....	1,080	2,700	1,050	June 23.....	840	2,830	1,650
June 6.....	2,520	2,370	690	June 24.....	240	2,130	1,530
June 7.....	780	3,210	1,110	June 25.....		2,800	1,170
June 8.....	3,000	3,030	840	June 26.....	420	1,620	1,380
June 9.....	1,020	3,840	915	June 27.....			
June 10.....	2,100	2,640	990	June 28.....	0		
June 11.....	2,160	3,340	645				
				Total.....	52,750		

SUMMARY

(1) A case of traumatic chylothorax is presented; there are already 45 well-authenticated cases on record.

(2) The etiology and clinical characteristics are quite typical and constant in the cases reported.

(3) A careful analysis of the aspirated fluid is essential in making the diagnosis.

(4) The best method of treatment is still speculative, although the present case seems to indicate the advantage of conservatism.

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SURGICAL ASPECTS OF BLEEDING GASTRIC AND DUODENAL ULCER*

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DURING the past ten years, 1924 to 1933 inclusive, 50 cases of gastro-duodenal ulcer complicated by hemorrhage have been treated at St. Luke's Hospital. Our interest, at this time, attends bleeding from the stomach and duodenum only, and question of differential diagnosis as to the source of the hemorrhage will not be considered. Where there has existed a doubt as to the origin of the hemorrhage, that case has been excluded from this study.

Moynihan[1] states that hemorrhage is usually a late symptom which indicates that the ulceration has penetrated the deeper layers, eroding a blood vessel. Hemorrhage occurred in 37.6 per cent of his cases, which is somewhat more frequently than is usually found. I find the incidence to be approximately 12 per cent. He mentions three cases in which death from hemorrhage occurred before surgical help could be given, and this is not unusual.

Although massive hemorrhage, as the result of the erosion of a large vessel in a deeply penetrating ulcer, does occur, it is comparatively rare. I found massive hemorrhage due to erosion of a large vessel in only three cases: one in ulcer on the posterior surface of the duodenum associated with advanced carcinoma of the head of the pancreas; one in a deeply penetrating ulcer on the posterior aspect of the lesser curvature; and the last (following treatment for esophageal stricture) where strings, swallowed and retained in the stomach and duodenum, had incised the wall of a large artery. In this series there were nine penetrating ulcers on the lesser curvature and in eight of these the bleeding was slow, continuous, over long periods and resulted in extreme secondary anemia. On the other hand, in every case of proven duodenal lesion the hemorrhage was massive and recurrent. Perforation of duodenal ulcer on the anterior surface of the first portion, where penetration is complete, is not accompanied by hemorrhage. In three cases where perforation of an ulcer of the anterior surface occurred and was treated (in one instance by simple closure and in two by closure and posterior gastro-enterostomy) hemorrhage appeared later. It is fair to assume in each instance that there existed an additional ulcer on the posterior surface. This was the lesion found at autopsy in the first of these cases three months after closure.

An analysis of a series of cases in which there is massive hemorrhage from the duodenum leads one to believe that the physical characteristics of

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the second portion of the duodenum lend themselves to this phenomenon and that the etiology is an irritation of the mucosa with localized areas showing excessive excoriation which bleed copiously. Possibly this is a severe grade of duodenitis. Levine[2] has found that inflammation of the duodenum, with and without erosion, may be caused by a single factor or a combination of factors such as trauma from within and without, high temperatures, strong acids and alkalis, functional disturbances and allergic reactions. W. J. Mayo[3] states that in some of the chronic forms of duodenitis or ulcerative duodenitis the gross section looks like an ulcer, but on closer examination there is a moth-eaten appearance instead of a regular punched-out crater. And finally Wellbroch[4] has pointed out that some cases which are diagnosed duodenal ulcer at operation show an area of localized thickening of the duodenal wall instead of a definite ulcer. The thickened area is designated as occurring in various forms: as simple duodenitis; duodenitis with erosion or ulceration; and chronic duodenitis.

If ulcer situated on the first one and one-half inches of the duodenum and in the stomach is caused by the occlusion of the terminal vessels entering the muscularis mucosa, as has been shown by the experimentation of Virchow and Conheim,[5] it becomes apparent that the bleeding ulcer of the posterior surface of the second portion of the duodenum is a separate and distinct pathologic entity.

A brief description[6, 7] of the blood supply of the second portion of the duodenum will demonstrate the possibility of severe hemorrhage from this area. The duodenum, except for the first one and one-half inches, receives its blood supply from the superior and inferior pancreatico-duodenal arteries. Their anterior and posterior branches anastomose and make two arcades in the curvature of the duodenum and encircle the bowel. These pierce the muscularis and form anastomosing arcades in the submucosa. This insures a constant blood supply to all parts of the mucosa. The greater part of the blood supply is carried to the mucosa through two sets of arteries: one to the villi and one to the lower ends of the crypts, supplying both glands and stroma. Those to the villi (usually one to each villus) run through their centers, terminating in capillary networks at the summits. Thus an extremely vascular area is provided.

This is in contradistinction to the blood supply of the first one and one-half inches of the duodenum, where branches are given off from the submucous plexus to the mucosa, simulating to a marked degree the vessels of the stomach, but they are neither as long nor as tortuous. The submucous plexus is made up of small perforating branches. These make few anastomoses and run long distances. They enter the mucosa as terminal arteries connected only by minute capillary networks and every end artery supplies about 2.5 Mm. of mucosa.

Failure to deal satisfactorily with cases manifesting severe hemorrhage from the duodenum is due primarily to the reluctance on the part of the surgeon to interfere in the absence of definite clinical evidence of an exist-

ing lesion, specifically the absence of a demonstrable crater in one or more roentgen ray films. Unfortunately, this evidence is rarely at hand for in many instances the patient's condition does not warrant the risk of the manipulation of roentgen ray examination. Such examinations, as well as the recovery of the test meal, have caused further hemorrhage. After the patient's admission to the hospital for ulcer treatment I have seen the initial hemorrhage appear while the patient was undergoing these examinations.

To distinguish clinically between duodenitis and ulcer on the posterior surface is most difficult. Massive hemorrhage may occur in either case. Rivers[8] reports gross hemorrhage in 12 per cent of his cases of duodenitis. Judd and Nagel[9] were especially impressed by the frequency with which duodenitis is encountered and by the constant association of ulcer and an area of duodenitis on the posterior mucous surface which bleeds most easily. In this series it is probable, from the evidence, that duodenitis was the pathologic condition in 16 cases, in addition to those presenting ulcer of posterior surface at operation or autopsy.

The points on which a diagnosis may be based are: (1) history of indiscretion in diet followed by epigastric distress (70 per cent of the cases in this series admitted free use of alcohol); (2) complete failure of treatment by diet,[10] rest and alkalis; (3) massive hemorrhage in the absence of demonstrable lesion by roentgen ray examination; (4) recurrence of hemorrhage following gastro-enterostomy where marginal ulcer does not exist.

However, quite recently Kirklin[11] has shown that the characteristic roentgenologic findings in duodenitis are: a varying degree of increased irritability of the duodenum; a deformity of the bulb which is transient, without the characteristic density of ulcer; absence of ulcer crater; and finally absence of gastric retention. These characteristics are demonstrated in a film from one of our cases (Fig. 1). In 16 cases in this series the roentgen ray findings have suggested this condition. Findings of a similar nature, in cases presenting massive hemorrhage, should make one extremely suspicious of the duodenum.

Of the patients admitted to the hospital during the past ten years with gastroduodenal ulcer, approximately 12 per cent have been complicated by hemorrhage. In 75 per cent of these cases the hemorrhage has been massive and recurrent. In every case transfusion has been given at least once, and frequently more often, either during the course of a medical régime or as a preoperative or postoperative measure. These records show conclusively that transfusion has been completely ineffectual as a means of stopping hemorrhage.

Question as to the advisability of operation during the hemorrhage if it continues unduly, or immediately following, is a highly debatable one and I fully appreciate that prevailing opinion is opposed to it. However, hemorrhage of such proportions occurring elsewhere in the body is always treated as a surgical emergency and successful outcome is the rule. I find that patients operated upon under these circumstances have survived. One im-

mediate death occurred in a case complicated by carcinoma of the pancreas. In each instance where the operation performed was of the indirect type it was not surprising that the hemorrhage continued. I am of the opinion that immediate surgery of the direct type is justifiable in a large percentage of these cases and will prove permanently successful. The presence[12] of the lesion can be determined only by careful inspection at operation with the

FIG. 1.—Illustrating spasticity of the duodenum and transient bulbar deformity.

duodenum open. Preoperative and postoperative transfusions are an absolute requirement of this procedure. Inasmuch as ten cases in this series died in the hospital from continued hemorrhage while receiving most rigid medical treatment and, in many cases, daily transfusions, the above opinion seems warranted.

Of course I appreciate that certain cases of this type do have remissions and that one is influenced to delay operation in that hope, but many times

another hemorrhage follows very soon and the opportunity to operate under fairly favorable conditions is never again presented.

Nine cases in this group presented ulcer of the lesser curvature of the penetrating type. Seven were proven by roentgen ray examination and operation and two by autopsy. In eight of these cases there was no massive hemorrhage. The bleeding was slow and continuous over long periods, resulting in severe anemia. Three cases in this group were not operated upon. One case treated medically was discharged improved and not followed. A second died while under hospital treatment. A third, considered a bad surgical risk, died in the hospital under like conditions. Six cases were treated surgically and in each the ulcer was excised. Posterior Pólya was used four times with one immediate death. In two cases posterior gastro-enterostomy with excision of the ulcer was the procedure. These cases are well at the present time and have had no further bleeding.

Forty cases are found in which the evidence, clinical or positive, is sufficient to localize the lesion in the duodenum. Posterior surface ulcer was demonstrated nine times at operation and four times at autopsy. The history, symptoms and roentgen ray findings strongly suggest a similar pathology in 16 additional cases. Marginal ulcer was the source of hemorrhage in two cases. In every case the hemorrhage was gross, of sudden onset and recurrent. The blood appeared as hematemesis and in the stool.

In the analysis of the mortality and recurrence statistics relative to this group of cases (Table I) I wish to explain that the figures have been obtained from both the hospital records and the follow-up records. I feel that failure to arrest hemorrhage permanently by the therapy applied should be classified as recurrence and death from hemorrhage should affect the mortality statistics whether it occurs in or after discharge from the hospital. Under results as given in Table I "recurrence" refers to hemorrhage and not to ulcer symptoms. "Death" in each instance has been the result of another hemorrhage except where it occurred immediately postoperative. Twenty-six cases in this series are alive at the present time to the best of our knowledge. Eighteen of these have attended our follow up clinic during the past three months or have been reported upon by their own physicians.

Fourteen cases in the series were not operated upon while under hospital care or direction. Included are three cases in which the risk involved rendered surgical intervention out of the question. Thus eleven cases were treated medically and all received one or more transfusions. Seven cases have had one or more recurrences of hemorrhage and there have been eight deaths. Of course some of the fatalities have been among the recurrences.

Twenty-six cases were treated surgically, a total of 42 operations being performed either at St. Luke's Hospital or elsewhere. Reference to Table I will clearly indicate the events which have led to the use of so many operative procedures in attempts to stop recurrent hemorrhage. This factor has had a distinctly unfavorable influence upon our statistics.

TABLE I

Analysis of Recurrence and Mortality Statistics

Lesion	Roentgen Ray	Operation	Result
Duod. ant. and post.	Duod. deform.	(a) P. G-E (b) Exp. and app. (c) Pólya	Recurrence Recurrence Cure 3 years
Duodenitis and post. ulcer	Spastic duod., no crater	(a) Pyloroplasty (b) Exp. gastrostomy (c) Medical	Recurrence Recurrence 3 recurrences
Duodenitis and post. surf.	Spasticity, suspicious duod., lesion, no crater	(a) Explor. app. (b) P. G-E (c) Medical	Recurrence Recurrence 2 recurrences
Post. surf.	Duod. involv.	(a) Explor.	Recurrence
Ant. surf.	Deformed cap	(a) Medical (b) P. G-E (c) Jejunostomy (d) Explor.	Recurrence Recurrence Recurrence Op. death
Ant. perf. post. surf.	Duod. deform. after closure	(a) Clos. perf. (b) P. G-E (c) Explor.	Fol. by hemorr. Recurrence Op. death
Post. surf.	Gross duod. deform.	(a) Explor. (b) Pólya	Recurrence Cure 1½ years
Post. surf.	Spasticity of duod., no crater	(a) Pólya	Death
Post. surf. autopsy	Not done	(a) Jejunostomy	Death (volvulus)
Ant. perf. post. surf.	Not done	(a) Closure, P. G-E (b) Medical	9 recurrences
Ant. surf.	Duod. deform.	(a) Explor. (b) Medical	Recurrence Death
Ant. perf. post. surf.	Duod. deform.	(a) Closure (b) Pyloric reconstruction with cautery	Recurrence Cure 2 years
Post. surf. cholecystitis	Not done	(a) Jejunostomy (b) Pólya, cholecystectomy	Cure 18 months
Ant. perf.	Not done	(a) Closure (b) Medical	Death 3 months
Ant. surf. post. surf.(?)	Fol. P. G-E, rapid emptying	(a) P. G-E (b) Medical	Recurrence Recurrence
Ant. post.	Deform. cap	(a) Medical (b) Explor.	Continued hemorr. Death (op.)
Post. and ca. pancreas	Duod. deform.	(a) Cholecyst-gastrostomy, P. G-E	Death (op.)

TABLE I (*Continued*)

Lesion	Roentgen Ray	Operation	Result
Post. surf.	Empt. through duod. and stoma	(a) P. G-E (b) 2nd P. G-E (c) Undoing 1st (d) Undoing 2nd	Recurrence Recurrence Recurrence Death
Ant. scar, post.	Spastic duod.	(a) P. G-E	Recurrence with death (6 months)
Ant. perf. marg.	Marg. ulcer	(a) Closure (b) Undoing P. G-E	Well 3 years
Ant.(?) post.	Spasticity duod., no crater	(a) P. G-E (b) Medical	Recurrence Death
Ant. scar duodenitis	Spasticity and rapid emptying	(a) P. G-E (b) Medical	Recurrence Death
Post. surf. autopsy	Budding defect, less. curv., functioning stoma	(a) P. G-E (b) Lysis of adhes. (c) Medical	Recurrence Recurrence Death
Ant. surf.(?)	Duod. spasticity, rapid emptying	(a) P. G-E (b) Medical	Recurrence Recurrence
Post. surf.	Not done	(a) P. G-E for pylor. stenosis at 6 weeks	Massive hemorrhage at 18 years, none since
Ant. pert. post. surf.	Spasticity duod. deform., rapid emptying	(a) Closure with P. G-E (b) Medical	Recurrence Recurrence

Posterior gastro-enterostomy was the operation elected 17 times. There was no instance in which exploration of the duodenum was described as part of the operation. On several occasions a lesion, or the scar of a previous lesion on the anterior surface was described. This operation was followed by recurrence in every case. Twice the source of recurrent hemorrhage was found to be marginal ulcer. In nine cases postoperative roentgen ray examination showed a properly functioning stoma with free passage of the meal. This would indicate that the failure does not lie with the technic of the operation, but with its selection as the proper procedure to cure duodenal hemorrhage. Posterior Pólya was performed four times. There was one immediate death. The surviving cases have remained free of both digestive symptoms and recurrent hemorrhage. Pyloric reconstruction was used in two cases. In one there have been several recurrent hemorrhages treated medically, in the other an ulcer on the posterior surface was discovered and cauterized. This latter case has remained well for two and one-half years.

Galibladder disease was found three times in this series. Twice it was associated with ulcer on the posterior surface and removed in the course of the operation. In the third case it was the only demonstrable lesion, and this patient has had no recurrence and is well after eight years.

We find, in analyzing the surgical results in this group of cases, that

there has been recurrence following 24 of the operative procedures employed. Death has occurred as a direct result of operation or hemorrhage following surgical treatment in 13 cases, a mortality of 32.5 per cent.

It is my opinion that these results in the treatment of massive duodenal hemorrhage need not be duplicated if it is realized that this hemorrhage can be controlled only by direct surgical methods and that, in the absence of positive evidence of a lesion elsewhere, the source will be found on the posterior surface. The operation must be of a type which will deflect the food stream entirely and permanently from the duodenum. Indirect surgical treatment has proven unsatisfactory.

Although pyloric reconstruction is accompanied by very slight risk and gives opportunity to deal with the ulcer directly, it does not appear to me to insure against further hemorrhage. Resection of the Pólya type, to include the ulcer-bearing area wherever possible, has given us the most satisfactory end-results. Where risk becomes significant, resection for exclusion may be carried out with little, if any, more risk than gastro-enterostomy. Completely arresting gastroduodenal function by jejunostomy offers a primary procedure to arrest the hemorrhage and will permit early radical operation. I do not suggest this, however, as a routine procedure. I have used it three times, and in two cases I was able to do a resection successfully after three weeks. In the third case volvulus of a loop of intestine occurred on the fourth postoperative day, resulting in death.

CONCLUSIONS.—The source of massive hemorrhage which complicates gastroduodenal ulcer is from the posterior surface of the duodenum in a large majority of cases. The blood supply of this area makes gross hemorrhage possible without deep penetration of the wall. Definite exploration of the open duodenum is necessary to determine this source in all cases except those presenting large penetrating ulcers of the crater type. Preoperative diagnosis is usually definite in these cases, but diagnosis of the posterior surface ulcer is extremely difficult and, with our present facilities, can not be definitely accurate. However, early operative interference appears justifiable. That type of operation which completely protects the duodenum from further insult will effect the largest number of cures.

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DISCUSSION.—DR. JOHN DOUGLAS (New York) thought that Doctor Westermann had shown a great deal of courage in presenting so controversial a subject. He had also shown courage in presenting the most appalling statistics to which Doctor Douglas had ever listened. Doctor Westermann's thesis was that bleeding duodenal ulcers should be operated on, and that the operation should be a radical one consisting of partial gastrectomy. Statistically, Doctor Douglas thought Doctor Westermann had proved this. He cited 11 cases that were under medical treatment—the most adequate, he was sure, that could be given—with numerous transfusions; yet, five deaths occurred out of these 11 cases and three deaths occurred before any adequate treatment could be given. In other words, eight out of 14 cases died. No surgical statistics could be worse than that.

When Doctor Westermann spoke of the indirect method of treatment he meant gastro-enterostomy, and following that, according to his statistics, there was 100 per cent recurrence of bleeding. Methods of pyloroplasty have not been very successful either. Therefore, "statistically" he had proved his thesis.

The difficulty is that individual patients are not treated statistically. We all have more or less preconceived opinions. He could remember cases which had recovered after repeated transfusions, sometimes 10 or 12; and other cases—one in particular, not done at St. Luke's Hospital, who was operated on during acute hemorrhage after repeated transfusions in which the man leaked out blood as fast as it was put in. The operation consisted of excision of the ulcer, which was a large one on the posterior surface, and pyloroplasty; that man has had no recurrence. Another patient with repeated hemorrhages had ten transfusions, no operation, and has been well since then. He concurred with the internist that when a case is bleeding it is difficult for us to accept the statistical point of view and offer him an operative procedure which we are pretty sure is apt to have a high mortality. Doctor Westermann has not had a very much better mortality for his Pólya resections of the stomach during the hemorrhage. His mortality for the Pólyas is one out of four, which is 25 per cent, and his mortality for his jejunostomies is one out of three, which is 33 per cent. Naturally, we hesitate to advise operation where we feel there is a danger of 25 to 33 per cent mortality. At the same time, Doctor Westermann has made a very strong case for the futility of gastro-enterostomy in the instance of bleeding duodenal ulcer. We have got to have a little more fortitude and accept the surgical mortality in a certain number of these cases. If we are willing to do so, after repeated transfusions by means of which we have brought the patient up to the highest possible point before he starts sliding down hill again, he believed more patient's lives would be saved even if the surgeon receives a little more criticism for performing risky operations.

Doctor Westermann has rendered a valuable service in reporting these very bad statistics, which will give us a little more courage to advise operation and be willing to take risks. It is only fair, however, in the consideration of his statistics and reported cases, to remember that many of the deaths or recurrences of hemorrhage occurred after the patient left the hospital and the unfavorable or fatal results in the report are the result of a careful follow up.

DR. J. WILLIAM HINTON (New York) agreed with most of what Doctor Westermann had said. In an attempt to classify these bleeding ulcers, we had gone over 87 patients in the Fourth Division of Bellevue in the last 20 years and had accepted only gross hemorrhages where there was marked secondary anemia and shock, with transfusions indicated. There were nine deaths in the 87 cases treated conservatively, or 10 per cent mortality.

The division of these cases into groups was merely a means to help us to treat them. In the first of five groups we included patients who had been under adequate medical treatment and all of whom we considered to be absolute surgical cases because they had failed while under medical treatment. There were 16 patients in this group.

In the second group, we included patients previously operated upon for chronic ulcer without any history of bleeding, some of the 11 patients in the group having been operated on as long as 18 years before, others only a few months before the occurrence of a severe gastric hemorrhage. The treatment of these patients was conservative.

There were five patients in the third group, including cases previously operated upon for bleeding ulcers who had continued to bleed. Most of these five cases underwent a conservative type of operation, although in one instance a pyloroplasty was done and in another, a gastric resection. In the last two cases mentioned, bleeding recurred.

In the fourth group, patients were included who had no gastric history at all. There were 17 of these patients who had collapsed in the street and were brought in, in severe shock. In this group we had our highest mortality, nine of the 17 dying.

In the last group, consisting of 38 cases, there was a long gastric history. The patients had not received adequate medical treatment and so we did not advise surgery, although some of these cases have been operated upon.

It is a very difficult problem to direct the treatment for the individual person according to the cases we have followed. There is a patient now in the Fourth Division wards who illustrates very well the point Doctor Westermann brought out. This man was operated on out West for an ulcer, in 1926, and none was found. He continued to have symptoms and entered Bellevue in October, 1934, with a hemorrhage. He was explored with negative findings, and was referred to the clinic. His roentgenographic check up now shows a duodenal ulcer, and a week ago he reentered the hospital because of severe pain. Soon after coming in he developed a hemorrhage. He has a posterior duodenal ulcer so small that it could not be found at the first operation. The only way to attack it will be by a radical procedure.

Dr. John A. McCreery (New York) thought that the paper should have been presented before a joint medical and surgical audience, as his experience has been that most of these cases of acute bleeding ulcer are originally treated on the medical service and are transferred to the surgical service only when they are *in extremis*.

Doctor Westermann described the pathology and the anatomy. His impression had been from cases seen at Bellevue either at operation or postmortem that the major bleeding cases are those in which there is a deep penetrating ulcer rather than a mucosal erosion from chronic duodenitis. He supposed that the distrust of surgery in these cases is in part due to the fact that the diagnosis is so difficult to make. The patients usually come in as emergencies. Many have not been studied in the radiographic department before and the determination of the site of the ulcer is difficult. Also, in the past at least, when surgery has been attempted it has been a palliative, nonradical type of operation which, as Doctor Westermann has shown, is bound to have unsatisfactory results. It is not difficult to look up a series of statistics and decide in general what one should do, but when one is faced with an individual case one forgets statistics and makes an individual decision. If operation is to be done, however, he feels it must be a radical resection, as Doctor Lewisohn has done, at least in the doudenal case. He has seen one or two

cases of hemorrhage from ulcer on the lesser curvature in patients in poor condition, in whom the hemorrhage apparently was controlled by ligation of the artery on either side of the ulcer.

Doctor Hinton spoke of a patient in whom exploration had been negative. He was interested to hear him mention that case because he had a similar experience eight or nine years ago. The patient was admitted to the First Division, Surgical Service, with acute hemorrhage. They treated him medically and built him up so that in the course of time they could get radiograms and determine the site of the lesion. They brought his blood up to a reasonable level, but before the examination could be made he had another major hemorrhage. They treated him again medically and the day before he was to have his radiographic examination he had another hemorrhage. Although they did not know where the ulcer was, they operated. There was no evidence of ulcer. He opened the stomach widely enough to get his hand in, stretching the incision so that he could practically turn the stomach inside out, and still he found no evidence of ulcer. There was nothing in the duodenum either. Since then he has seen him at intervals of six months to a year and he has had no further evidence of bleeding.

He thinks Doctor Westermann has opened a new field, or perhaps an extension of an old field, in which we may be able to cut down the mortality which Doctor Douglas says is appalling.

Dr. John E. Jennings (Brooklyn) felt from his own experience that the "nigger in this woodpile" is transfusion to a very large extent. The Mayos stated the mortality of gastric and duodenal hemorrhage was 2 per cent if they were left alone. That was from an experience not exactly the same as ours because people do not go out to Rochester bleeding as did the 17 people who dropped in the street, mentioned by Doctor Hinton. But I think there is a good deal more in that point of view than we have realized. The man who drops in the street in collapse runs several hazards if he is to come out alive. The first one is the probability that he will be given transfusions as soon as he comes into the hospital, and I should say he has at least 25 per cent chance of being killed by that. If he avoids that, as an immediate affair, what is his next chance of dying? Operation before he is fit to withstand the results of his immediate shock, and hemorrhage. The third hazard is that when operated on he will not have anything done for him that will do him any good. That is, he will have a gastro-enterostomy done, and without any secondary care. If he comes finally to the last chance of major surgery, he has in that about 33⅓ per cent chance of getting by. Why not let him alone, then, until he stops bleeding? They abandoned transfusions in the Surgical Service of Cumberland Hospital three years ago and have not had a death from hemorrhage since.

Doctor Lewisohn (New York) thought that the surgeons are just as much to blame for the high mortality in bleeding ulcers as the physicians. Everybody is afraid of the high surgical mortality in this group of cases. They know that in the majority of bleeding ulcers the hemorrhage stops automatically. However, a number of cases will bleed to death without surgical intervention. Whereas the medical mortality in continuously bleeding ulcers is 100 per cent, surgery offers the patient the possibility of a cure.

In answer to Doctor Jennings' statement about the harmfulness of transfusions, he would like to emphasize that a transfusion given at the proper time is most beneficial and often lifesaving.

Dr. Henry F. Graham (Brooklyn) thought that the New York Surgical

Society should not go on record as approving gastric resection in every case of bleeding ulcer. He had had two cases cured without resection. Some years ago a patient received repeated transfusions but died after an operation at which they were unable to find any ulcer. Nothing could be found at autopsy, either, until they had taken out the stomach and all the intestines and opened them from the cardia well down into the jejunum. A tiny slit was found in a vein on the mesial side of the duodenum without any induration around it.

Shortly afterward, another case came in with hemorrhage and, after a few transfusions, was operated on. The site of the bleeding in the first case was first examined to see if there was anything there in this instance. There was some induration on the mesial side of the duodenum, second portion, and since most of the blood supply of the duodenum is from the pancreatico-duodenal and gastroduodenal vessels on the inner side, it seemed to him there was no reason why he could not stop the bleeding by ligation there as in any other part of the body. A suture was placed around first to get good constriction, then a gastro-enterostomy was done. He kept track of this patient for many years, during which he remained well and free from any further hemorrhage.

Another type of case in which gastric resection is certainly inadvisable is illustrated by a patient in whom the ulcer was so high that such a radical procedure would not be warranted because of the general debilitated condition, in which instance a cure was effected by electrocauterizing the edges of the ulcer and infolding it.

Doctor Westermann wished to point out that this type of ulcer is possibly a duodenitis. Further study of duodenitis may enable one to discover the reason for the bleeding. He thought Doctor Jennings' first two cases demonstrated this very clearly. The first case he presented was decidedly associated with Banti's disease; one of their cases associated with cirrhosis of the liver was similar. There is a disturbance in the chemistry of the body at such times and this type of bleeding must be distinguished from the bleeding of definite duodenal lesions. In the second case, he believes there was a disturbance of the physical characteristics of the stomach and duodenum resulting in disturbed gastric digestion with its insult to the duodenum. We see this in certain cases of diseased gallbladders with adhesions; when the gallbladder is removed the duodenal irritation is relieved.

Duodenitis is becoming more and more recognized as a distinct entity. Recent studies show that there is massive hemorrhage in from 14 to 20 per cent of these cases. In many cases of penetrating ulcer on the lesser curvature they have done a posterior gastro-enterostomy with excision. The results have been satisfactory.

SPONTANEOUS RUPTURE OF A NORMAL SPLEEN

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CAREFUL review of the literature reveals only two cases of spontaneous rupture of an apparently normal spleen. Spontaneous rupture of the spleen not uncommonly occurs, but, aside from the two above mentioned cases, always in a spleen already enlarged as a result of preexisting disease. Malaria is the most frequent cause. Berger[1] found 132 reported cases prior to 1902 and of these ninety-three ruptures were caused by malaria. In fifteen the spleen was simply reported enlarged but no special pathology was mentioned. Of the remainder nine were incidental to pregnancy, five occurred following typhoid fever, three in leukemia, and one each in pneumonia, hereditary syphilis, alcoholic cirrhosis, tuberculosis, hemophilia and varices of the capsule of the spleen. Infarct, abscess and aneurysm have also been noted. Leighton[2] collected the records of seventy-three cases from all causes and reported one of his own due to malaria. Conner and Downes[3] reported a spontaneous rupture from typhoid and reviewed records of twelve others. More recently Haines and McIlroy[4] reported a case of spontaneous rupture of the spleen due to a cavernous angioma. They quote Ewing[5] to the effect that there are on record thirteen cases from the same cause through 1913. Moynihan[6] states that the literature records only the three cases reported by Cannaday, Shorten and Connors in which the spleen was apparently normal in size and texture.

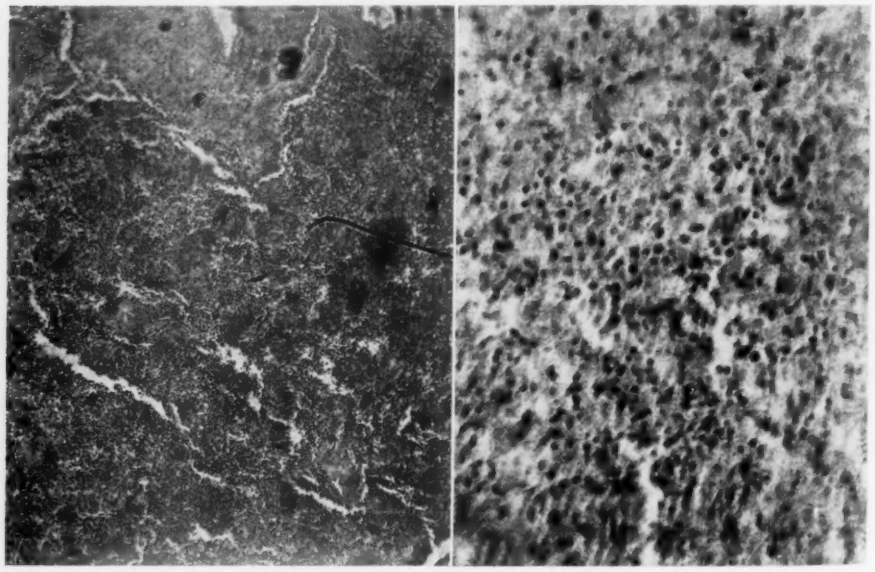
Cannaday[7] actually reported the second case of spontaneous rupture of a tuberculous spleen, the first being that reported by Aufract and included among Berger's 132 cases. In describing the spleen Cannaday writes, "There were numerous tubercles on its surface. In the body of the viscus there were a number of pockets containing caseous material. In some parts of the organ there were calcareous deposits also. The caseous masses varied from 1 cm. to 2.5 cm. in diameter." In this case there was also a tuberculous right kidney which was probably the cause of the patient's death three months after the splenectomy. The exclusion of this case then leaves only those of Shorten and Connors to be properly classified as spontaneous ruptures of the normal spleen.

Shorten's[8] patient was a private in the B. E. F., a man forty-three years of age, whose past history was negative except for a chronic bronchitis. About a year before he had been buried in a trench. Following this experience he suffered from some slight abdominal discomfort which Shorten believed had no connection with the subsequent rupture. The patient had never had malaria nor had he ever been in a malarial country. While walking to his billet he was seized with a sudden pain about the umbilicus. The severity of the pain caused him to fall to the ground. Operation was performed for a ruptured abdominal viscus. The abdomen was found full of fluid blood with many clots in the splenic fossa. The spleen itself was divided into two almost equal portions; the gall-bladder was full of stones but was not removed, because of the patient's grave condition. Microscopic examination of the spleen showed it to be normal. No blood

counts were made. The suggestion was made that the pain about the umbilicus was due to gallstone colic and that the rupture of the spleen was traumatic, occurring after the fall. The author discounted the explanation after careful questioning of the soldier, who denied any previous trauma and who stated that the ground on which he fell was level and contained no rocks. Shorten moreover found no marks of external injury and felt forced to report the occurrence as a spontaneous rupture of a normal spleen.

FIG. 1.—Gross specimen showing explosive tear in capsule of spleen and the retraction of the capsule. The dark portion is the exposed splenic pulp.

Connors[9] case reported from this hospital was a man thirty-eight years of age, a driver by occupation. He had recently been a patient in another hospital. There he had been treated for bronchitis, which, he was told, might develop into tuberculosis. He was also addicted to periodic sprees. The patient was admitted to the hospital complaining of pain in the region of the right hypochondrium for three weeks. He was markedly constipated. Roentgen ray showed obstruction in the neighborhood of the splenic colon. On the day before operation, the patient complained of pain in the left side. At



FIGS. 2 and 3.—Showing low and high power fields. Both sections are those of normal spleen pulp.

operation, performed for malignancy of the large bowel, the splenic flexure was normal. On displacing it downward a large hematoma was found which ruptured on being touched. The spleen was bisected, the hematoma having been held intact by the stretched splenic capsule. Three months later Connors reoperated on this patient, who returned to

the hospital with a complaint similar to the first—pain in the left hypochondrium. A large quantity of chocolate-colored fluid was evacuated from what was evidently a pancreatic cyst resulting from injury to the tail of the pancreas at the first operation. He died four years later of pulmonary tuberculosis. In commenting on this case Connors writes that the spleen was grossly normal in size and texture. No microscopic examination was made because the specimen was unfortunately lost between the operating room and the laboratory.

CASE REPORT.—Patient E. B., a full-blooded American Indian, forty-seven years of age, a clothes presser by occupation, was admitted to Harlem Hospital March 31, 1933, complaining of abdominal pain of six hours' duration. At 5 P.M. on the afternoon of admission, while pressing a coat, patient felt a sharp pain in the right lower quadrant. This pain was not very severe and he continued working. About twenty minutes later he felt an excruciating pain below the left costal margin. This time, he said, "the pain doubled me up and cut my breath off." At 5:30 P.M. he had a loose bowel movement which did not contain blood. He vomited soon after admission.

Previous History.—Patient was born in Washington, D. C., has lived in New York City since the age of three. He has never left this city except for a short trip to Canada; has never had malaria or typhoid fever. Appendectomy in 1905. Neisserian infection in 1910. Chancre in 1912. Smokes and drinks moderately. Eating habits irregular from economic pressure, usually eats one meal a day. He denied any association of pain or vomiting with meals and had not noticed any bloody or tarry stools.

Physical examination showed an acutely ill middle-aged man. The abdomen was rigid and tender throughout but the tenderness was most marked in the left hypochondrium and the right lower quadrant. Roentgen ray showed foci of tuberculosis in both lungs and a dense shadow under the leaf of the diaphragm. Urine was negative. The blood count was: R.B.C., 5,100,000; hemoglobin, 90 per cent.; W.B.C., 10,150; polynuclears, 79 per cent.; lymphocytes, 21 per cent.

Operation for ruptured gastric ulcer was performed immediately through a right rectus incision. On opening the abdomen fluid blood under tension escaped. Stomach and liver were normal. In the splenic fossa there were a large number of blood clots. Fresh bleeding could be seen coming from the surface of the spleen, which was removed. The abdomen was closed without drainage. During the operation an infusion of 750 cc. of 5 per cent glucose in saline was administered.

Pathologic Examination.—The specimen removed was a small spleen, 12 by 9 by 1 cm., weight 67 Gm. The surface was covered by a blood clot. The capsule was completely avulsed from the convex surface and was contracted about the pedicle. It is very soft and flabby. On section the splenic tissue has a dull reddish brown appearance. The trabeculæ stand out prominently. The malpighian bodies cannot be seen. There is also a large amount of blood clot. Doctor Weintraub, the pathologist, further claimed that the spleen was normal. Since this was undoubtedly a spontaneous rupture an exhaustive effort was made to determine the cause of rupture. A member of our pathologic staff took the specimen and slides to Mr. Sinai Hospital where it was again declared normal. Dr. Ralph Stillman, of Cornell University, examined the organ painstakingly but was unable to find any definite pathology. Dr. Douglas Symmers, Director of Laboratories at Bellevue Hospital, pronounced it an average spleen, normal for the age of the patient.

Postoperative course was uneventful except for some separation of the upper angle of the incision which necessitated a secondary repair on April 22. Connors[9] states that this wound digestion not infrequently follows splenectomy.

The blood showed rapid degeneration. The following count was made April 2, the day after operation: R.B.C., 3,300,000; hemoglobin, 66 per cent; platelets, 220,000; W.B.C., 11,000; polynuclears: staphylococcus cells, 50 per cent.; segmented, 32 per cent.; monocytes, 9 per cent.; lymphocytes, 9 per cent.

By April 6 the red cell count had risen to 4,010,000; hemoglobin, 75 per cent.; W.B.C., 8,400; polynuclears, 74 per cent.; lymphocytes, 26 per cent. The patient was

discharged May 9, 1933. I saw him again August 16. A blood count on that date showed continued improvement; R.B.C., 4,900,000; hemoglobin, 90 per cent.; W.B.C., 8,600; polynuclears, 66 per cent.; transitionals, 4 per cent.; lymphocytes, 30 per cent. At this examination he felt perfectly well and had no complaints.

Comment.—It may be of some significance that all three of these cases of spontaneous rupture of the normal spleen occurred in patients who had associated chronic pulmonary infections. In discussing chronic splenomegaly due to chronic passive congestion Poole and Stillman[10] list chronic pulmonary disease as one of the common causes. They consider that the congestion results from a combination of mechanical, chemical and toxic factors. Their description applies entirely to spleens removed at post-mortem.

The microscopic examination revealed the presence of surprisingly small increase in the fibrous tissue content of the spleen when one considers its extreme hardness in this condition. The capsule, trabeculæ, and the pulp reticulum all show but moderate increase in thickness. The pulp cords and the lymphoid tissue show little or no deviation from the normal. The striking feature in the picture is the tremendous engorgement of the spleen with blood. The venous sinuses are widely though rather irregularly dilated and their walls may be recognized only with difficulty. The pulp tissue is markedly infiltrated with red blood cells and the whole appearance has been called that of a blood lake.

It would appear that this picture of chronic passive congestion associated with pulmonary disease of long standing might suffice to explain the mechanism of rupture in these spleens which are apparently normal after rupture has taken place. There is even a strong possibility that Connors actually saw the so-called "blood lake" before the capsule broke. In my own case it is quite evident that some violent internal force such as increasing blood engorgement must have been at work to cause the explosive tear in the capsule that is shown in the specimen. I am at a loss, otherwise, to explain the rupture in this man who was perfectly well up to the time of rupture, who denied any trauma of any kind, who did not even fall to the floor but simply doubled himself up in a crouching position when seized with pain and whose body showed no external marks of injury. Following the splenectomy the patient has appeared to gain weight and is having no trouble from his pulmonary condition.

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GAS GANGRENE

A REVIEW OF SEVENTEEN CASES

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GAS gangrene is much less frequent in peace than in war. However, during a recent month three cases were admitted to the surgical service at the Knickerbocker Hospital, possibly the result of a wide experience in traumatic surgery which this institution enjoys. On this account, a review of the hospital records for the last decade has been made, in order to ascertain the number, variety and duration of such infections in a large metropolitan area. It was also thought that such a review might determine the efficiency of serum treatment, blood transfusion, and operative measures in a series of unselected cases in civil life.

While no definite conclusions can be based on a small number of cases, it is hoped that those herewith reported may serve a useful purpose. Clinically, several types are recognized: (1) Localized anaerobic infection of the wound. (2) Slowly spreading anaerobic infection in the wound. (3) Gas gangrene of the "group" type, where a single or a group of muscles only is attacked. (4) Gas gangrene of the massive type, where a whole segment of the limb is attacked. (5) The fulminating type, where an overwhelming infection and toxemia results fatally in twenty-four to forty-eight hours.

The complications of pyemia with metastatic abscess and septicemia with mixed infection of streptococci and staphylococci are not infrequent. The pathology of this disease has been well understood for years and the writers will therefore not dwell upon it, except when unusual features are presented.

The bacteriology also received such a thorough experimental and cultural investigation during the World War and the organisms were so conclusively identified, that nothing can be added to this study in cases in which the *Clostridium welchii* (perfringens) is the only organism isolated. In civil life in this country any other organism is rarely identified. This may be due to defective technic as in other countries one or more varieties of gas-forming organisms are usually present, making the treatment by Welch bacillus antitoxin alone less effective than by the polyvalent serum. In all seventeen cases, however, of which abstracts follow, the Welch bacillus alone was found. Tetanus, even in civil practice, is conspicuous by its absence. In war, it is believed that the prophylactic injection of tetanus antitoxin may have been largely responsible for its rarity. Association with other pathogenic organisms, *e.g.*, streptococci and staphylococci, is frequent and not rarely determines a fatal issue.

The importance of early and prompt diagnosis cannot be overestimated in

order that appropriate treatment can be carried out. Its occurrence is always to be feared in wounds complicated by impairment of the main or collateral circulation and especially by the extensive crushing of muscle tissue, associated with compound fractures. Exceptionally, as in other infections, gas gangrene may complicate simple lacerations, abrasions and burns and may even appear in ulcers.

The prophylaxis of gas gangrene by serum injections is the exception, possibly due to the prohibitive cost of the antitoxin. While a valuable adjuvant, it is in no sense a substitute for early and prompt surgical treatment.

The special signs of infection due to gas gangrene are pain in the region of a wound within a period of one to four days after an injury. This pain is sudden in onset and frequently much more intense than the condition of the wound would indicate. There is usually a foul, brownish, serosanguineous discharge with a peculiarly characteristic odor, which Ashhurst has described as that associated with a mouse, and in which bacteriologic examination reveals the presence of the gas bacillus. Frequently, within a few hours the more characteristic discharge with bubbles of gas, and liquefied fat, and the spreading crepitation which can be readily detected by palpation, auscultation and roentgen ray, develop and are followed by the usual indications of mortification.

CASE REPORTS

CASE I.—Male, white, nineteen years. Admitted to Knickerbocker Hospital January 10, 1924. Bath tub accident—fell in getting out, thrusting left arm through glass door, resulting in deep laceration left forearm. In attempting to stop bleeding, patient had applied rags and tied arm of bathrobe around arm. Patient given 1500 units of tetanus antitoxin on admission 1/10/24. Under general anesthesia vessels ligated, muscles sutured. Median and ulnar nerves found severed, no attempt made at suture. 1/11/24, dakinization of wound. Temp. rose to 104.6°, swelling and pain of forearm, culture negative for *C. welchii*. Later bubbles of gas from wound. Direct smear positive for *C. welchii*. Patient transferred to Roosevelt Hospital where an immediate débridement was done; patient eventually recovered without administration of antiserum. No attempt made at Roosevelt to suture nerves.

CASE II.—Male, white, fifty-three years. Admitted to Knickerbocker Hospital June 7, 1924. Tetanus antitoxin on admission. Three days before right arm crushed in vise-like machine just below shoulder joint. A severe infection had developed, also a state of shock was present on admission. Laceration of axilla down to nerves and muscles. No radial pulse obtained. Color of skin blue. Foul discharge gas in bubbles, crepitus. Temp. 104°, pulse 120. Cold sweat. 6/9/24, Disarticulation at right shoulder, affected muscles débrided, smears positive for G.B. and staphylococci. Peroxide dressings applied. Wound later dakinized. 6/26/24, Further débridement. Secondary suture, which later gave way allowing the skin margins to gape. Healed by granulation. 9/13/24, Discharged, wounds healed, no serum.

CASE III.—Male, white, thirty-six years. Admitted to Knickerbocker Hospital April 18, 1925. Tetanus antitoxin on admission. Right heel crushed by elevator, profuse bleeding controlled by tourniquet. *Diagnosis.*—Compound comminuted fracture of os calcis with upward displacement of posterior fragment, wound cleansed with benzene and alcohol and ether poured in. Rubber dam drain. Three silkworm sutures, large opening for drainage. 4/21/25, Temp., 103.4°. Complains of constant pain in region of wound. 4/26/25, Irrational. Temp., 104.4°. 4/27/25, Blood culture negative. 4/29/25, Tissues

about fracture gangrenous, sloughing, pus burrowing up leg, circular amputation below knee. 5/1/25, 400 cc. direct transfusion. Cultures positive for G.B. and staphylococci. 10/25/25, Revision of stump. 1/26/26, Discharged, stump healed, no serum treatment.

CASE IV.—Male, white, forty-four. Admitted to Knickerbocker Hospital Nov. 24, 1925, with compound fracture right tibia and fibula, and gas bacillus infection. Had received tetanus antitoxin at another hospital. Struck by automobile four days previously. Large wound anterior aspect of right leg, edematous and suppurating. Crepitation below wound. Positive culture for G.B. 11/24/25, Débridement; dakinization. 11/25/25, Dakin's sol. replaced by peroxide with encouraging results. Temp. and pulse continued high, irrational. 12/1/25, Foul smelling discharge. Extension upward of edema, redness and pain outer aspect of thigh, multiple incisions. Culture showed staph. and strep. Later pulmonary edema with hemoptysis. Temp. continued 102.6°. 12/11/25, Died.

CASE V.—Male, white, nine years. Admitted to Knickerbocker Hospital Aug. 30, 1927. Tetanus antitoxin on admission. Riding go-cart, struck elevated pillar, receiving deep 13-inch laceration mid third right leg external surface. 8/31/27, Débridement. Suture of peroneal group of muscles and tendon of peroneus longus tendon, skin closed with silkworm, adequate drainage. 9/1/27, Patient delirious. Temp. 106.4°, pulse 148, resp. 42. Wound has a foul smelling brownish discharge. Second débridement; all necrotic and affected tissues removed. Strict hemostasis; 200 cc. perfringens antitoxin intravenously. Smear shows organism morphologically identical to *C. welchii*, later confirmed by culture. Wound dakinized. 9/7/27, Wound negative for G.B. 9/20/27, skin grafted. 10/19/27, discharged healed.

CASE VI.—Male, white, thirty years. Admitted to Knickerbocker Hospital Oct. 16, 1927. Tetanus antitoxin on admission. Riding motorcycle, struck by automobile, sustaining compound comminuted fracture distal third, left tibia and fibula with internal and backward angulation. 10/16/27, débridement. Reduction of fracture. Six open wounds drained. Steinmann pin through os calcis. Thomas splint, Balkan frame, moderate traction. 10/17/27, Sutures removed. Serosanguineous discharge of foul odor. Smear and culture positive for *C. welchii*. Wound irrigated with peroxide. 10/20/27. Culture also positive for staphylococci. 10/26/27, Blood count 3,320,000, hemoglobin 67 per cent, leukocytes 16,800. Retention and traction cont., wound continued to suppurate. 11/7/27, Suppuration continued, wound has healthy granulations. 11/14/27, Blood count 12,400. Wound dakinized. 11/16/27, Traction removed. Drainage continued until date of discharge. 3/11/28, Patient went home in plaster case with window, and returned to dispensary. Healed after 3 months. No serum treatment.

CASE VII.—Male, white, forty-two years. Admitted to Knickerbocker Hospital May 25, 1929, tetanus antitoxin given. Spontaneous compound fracture of old ununited fract. rt. tibia. Leg "gave away" while standing. Fracture accompanied by pain and hemorrhage. On admission he presented a small lacerated wound on the external lateral aspect of the distal one-third of the leg. There was subcutaneous crepitation extending from the ankle joint to two inches below the knee. Also crepitus, mobility and displacement of the right tibia and fibula. 5/26/29, Multiple incisions for gas gangrene. Fifteen Carrel tubes inserted; muscles exposed looked like boiled ham; no bleeding; smear and culture positive for *C. welchii*. Condition of right leg continued to grow worse and on 6/19/29, under spinal anesthesia, amputation was done through upper one-third of leg. 10/11/29, After stormy convalescence, and later skin grafting; discharged. No serum treatment.

CASE VIII.—Male, white, fourteen years. Admitted to Knickerbocker Hospital Sept. 7, 1931. Stumbled, fell against spiked fence, sustaining transverse lacerations of the left biceps and the web space between the index and middle fingers right hand. Tetanus antitoxin given. 9/7/31, Biceps repaired and laceration of hand sutured. 9/9/31, Temp. 103°. Tissue about wound left arm edematous and crepitation present. Gas bubbles exude with greenish thick foul smelling discharge. Same condition present in right hand wound. Smear and culture positive for *C. welchii* both wounds. 9/9/31, Multiple in-

cisions left arm and right hand, packed with peroxide gauze. Forty units G.B. antitoxin intravenously, 60 intramuscularly. 9/10/31, tissues appear healthy, no gas or crepitation. Dakinization started. 9/18/31, Normal temperature. 9/28/31, Revision of wound left arm to approximate skin. 10/10/31, Discharged.

CASE IX.—Male, white, thirty-four years. Admitted to Knickerbocker Hospital, Dec. 19, 1931. Tetanus antitoxin four days before in emergency ward. Sustained laceration outer aspect right ankle, four days before admission. Wound had been sutured and drained at emergency ward of hospital. Attended to daily since. Wound remained tender and did not heal. Admitted to hospital on suspicion of G.B. infection. No temperature, presented laceration with necrotic base, no gas, no crepitus and slight foul smelling discharge. Smear and culture positive for *C. welchii*. 12/19/31, No separation, sutures removed. Peroxide dressing. 12/21/31, Wound scrubbed with soap and water, followed by alcohol; boric acid wet dressing. 12/23/31, Discharged to O.P.D. Wound granulating well, healing after ten days. No serum treatment.

CASE X.—Male, colored, thirty-two years. Admitted to Knickerbocker Hospital Aug. 8, 1932, with a badly compound comminuted fracture of lower third right tibia and fibula, and a history of leg having been crushed by an elevator. Tetanus antitoxin on admission. 8/8/32, Under spinal anestnesia, débridement of wound which extended upward from internal malleolus 4 inches. Necrotic tissue and dirt removed, also from wound over ext. malleolus. 8/8/32, Fractures were reduced by replacing comminuted fragments; circular case with fenestration for dressings at point of fracture. Temp. rose to 104.5° after operation, then receded to 100–102°. Bloody discharge from wound, positive for *C. welchii*. 8/11/32, Wassermann reported 3+. 8/12/32, case removed. Dakin's tubes inserted and dakinization commenced. 8/18/32, Volkman splint. Continuous saline irrigation of wounds. Neo-salvarsan and bismuth salycilate injections. 9/12/32, dichloramine T applied to wound and thereafter ultra violet and infra red both used on open wounds. 11/12/32, walking on crutches. Caliper splint. 12/24/32, discharged home.

CASE XI.—Female, colored, twenty-nine years. Admitted to Knickerbocker Hospital Nov. 27, 1932. Tetanus antitoxin on admission. Had kicked her right foot through glass door panel, sustaining deep lacerations lower third right calf. It bled profusely and tourniquet was applied to control it. Laceration 4 inches above malleoli, transverse 2 inches long severing tendon of gastrocnemius, also 3 inch vertical laceration forming L shaped wound with transverse laceration. 11/28/32, tenorrhaphy, myorrhaphy, repair of posterior tibial nerve, drainage, G. and E. anesthesia. 11/30/32, foul smelling, brownish discharge, bubbles coming from wound. Crepitation around wound. *C. welchii* found in smear and culture. Carrel tubes inserted, irrigation with peroxide. 12/1/32, temp. 103.8° Wound opened widely. Twelve Carrel tubes inserted in all deep areas, under fascia and muscles. 12/2/32, temp. 104°. Irrigation cont. with peroxide, no odor, no crepitus, slough separating leaving healthy granulations. 12/6/32, temp. down, acriflavine dressing, later red wash. 12/22/32, discharged, wound not entirely healed, able to move ankle in all directions. No serum treatment.

CASE XII.—Male, white, thirty-five years. Admitted to Knickerbocker Hospital Feb. 24, 1934. Tetanus antitoxin on admission. In coma, with traumatic amputation, lower third left leg and profuse hemorrhage, also lacerations of scalp and face. Alcoholic odor to breath. On account of coma, fractured skull was suspected but patient's condition did not allow roentgen ray examination on account of severe shock. Treated mainly for shock but without avail. Peroxide dressing to amputation. 2/25/34, transfusion 500 cc. 2/26/34, Very restless. Clysis 1,500 cc. glucose and saline. Foul odor noticed culture of serosanguineous discharge positive for *C. welchii*. Patient never recovered from shock and died fifty-two hours after admission. No definite treatment for G.B. infection.

CASE XIII.—Male, white, forty-five years. Admitted to Knickerbocker Hospital March 11, 1933. Varicose ulcers right leg, several small superficial ones on upper

anterior aspect of leg, two larger deeper ones with gangrenous base over each malleolus. The whole foot was edematous. Ulcers had been present for nine months. Two weeks before admission, patient had received at intervals two injections into varicose veins of the right leg. Patient had walked to hospital. Blue ointment applied and dry heat by cradle and lights. Patient restless, complaining of pain in right leg. 3/12/33, temp. 102°. 3/13/33, spinal tap negative. 3/15/33, culture for *B. welchii* taken. Gangrene spreading. 3/16/33, Patient restless, incoherent. Epistaxis. Temp. 105°, pulse 130, resp. 40, 60 c.. G.B. antitoxin intramuscularly, 500 cc. whole blood transfusion. 3/17/33, Culture positive for *C. welchii*. Temp. 101.8°. Amputation, guillotine, lower one-third thigh, gas anesthesia. Femur cut through 2½ inches above skin incision. Dakinization of wound. One amp. antitoxin in 500 cc. saline with 1 cc. adrenalin immediately after operation. 3/18/33, Wound clean. Dakins cont. Antitoxin. 3/24/33, same treatment, very restless, irrational, complaining of pain in thigh. 3/26/33, relapsed into stupor. 3/28/33, died.

Case XIV.—Male, white, fifty-two years. Admitted Knickerbocker Hospital Feb. 1, 1934. Tetanus antitoxin on admission. While unloading truck, struck by skidding automobile. Comp. fracture lower one-third right femur, profuse bleeding controlled by tourniquet. Deep laceration about 2 inches above right knee, 8 inches in length, marked shortening deformity abnormal motion and pain. Temporarily immobilized in Thomas splint with dressings. 2/2/34, roentgen ray showed comminuted fracture, junction middle and lower thirds right femur also the presence of gas, deeply located. Serosanguineous discharge of characteristic odor. Smear and culture positive for *C. welchii*. 2/2/34, (Dr. Armstrong) guillotine amputation right leg 4 inches below great trochanter. Ether anaesthesia. Immediate postoperative condition good, but treated for shock. Had received therapeutic dose of polyvalent serum intravenously before operation. This was continued daily thereafter. Had stormy convalescence, hiccough, skin reactions to serum, septic temperature. After six daily injections of serum intravenously further specific treatment discontinued. Traction applied to stump. 2/28/34, Patient became very anemic and 500 cc. transfusion given which was followed by chill and fever 106°. Wound finally cleaned up with acriflavine and dichloramine T. Bone protruding. 4/28/34, Stump revised, ¾ inches bone removed, no febrile reaction followed. 6/3/34, discharged stump healed.

The interesting features of this case were the typical anemia curve (Graph 1), as shown by blood counts and the fact that gas bacillus was cultivated from apparently healthy granulations until April 13.

Case XV.—Male, white, thirty-one years. Admitted to Knickerbocker Hospital Jan. 29, 1934. Boiler exploded, causing second and third degree burns of left hand and arm, right hand, left ankle and right leg and ankle. The force of the explosion hurled him against stairway, causing a large hematoma in right popliteal space. Treated for shock, given tetanus antitoxin, right leg. Immobilized with splint. 1/30/34, roentgen ray right negative, right foot and leg cold and cyanosed. Circulation definitely impaired. Eight-inch longitudinal incision of popliteal space. Blood clots removed, gastrocnemius muscle ruptured. No fresh bleeding, blood vessels thrombosed. 1/31/34, circulation not improved as result of operation. Patient complains of severe pain and sense of pressure in foot, very restless. Temp. 101°. 2/1/34, cyanosis of foot, and lower half of right leg. Considerable bleb formation extending almost to knee. Foot definitely gangrenous. No sensation or mobility of foot. Temp. 102°. 500 cc. whole blood by transfusion. Under spinal anesthesia, guillotine amputation through lower one-half thigh (Doctor Easton). On cutting through skin and muscle, escape of gas and liquified fat, characteristic odor of *C. welchii*. Crepitus extended subcutaneously to crest of ilium and Poupart's ligament. Muscles had normal color, good contractile power and bled readily, so that no attack was made higher up. After operation, ampule of polyvalent serum given, followed by another in 6 hours intravenously. 2/2/34, smear and culture positive for *C. welchii*. Two more ampules of antitoxin intravenously at six-hour intervals. After this, one ampule daily until Feb. 8. 2/4/34, dakinization of stump since operation. Healthy granulation.

Left arm entirely denuded by burns, treated with warm boric soaks, crepitus still present up to Poupart's. Temp. 102°. 2/9/34, Still slight crepitus below Poupart's. Culture still positive. 2/11/34, crepitus has disappeared. Temp. and blood count down. Wound culture loaded with short chain streptococci. No *C. welchii*. 2/15/34, wound still positive for *C. welchii*. Running some temp. again. Dichloramine T dressing. 10 pounds traction on stump. On account of recrudescence, more antitoxin was given.

The skin was tested for serum sensitization. Negative conjunctiva, very slightly positive skin test. Five cc. serum given in five minutes (five minutes after the administration of 10 minims of adrenalin) then 5 cc. more rapidly. At this point, patient said he had a bad taste in his mouth. There was a sudden convulsion and 2 cc. adrenalin was given at once. Patient promptly recovered. Ten minims adrenalin to be given every fifteen minutes for three doses. Blood pressure rose immediately following adrenalin to 300 systolic or above. Patient had received no gas bacillus antitoxin since February 7. When the injection of serum caused a severe anaphylactic shock marked by a very rapid and weak pulse, patient complained of a constriction in chest, dulled vision, and profuse sweating, later followed by chill and elevation of temperature, although this latter did not rise much higher than the daily excursion, 101° F. These alarming symptoms were fortunately relieved by the immediate hypodermic injection of adrenalin solution repeated within a few minutes. 2/17/34, traction brought down skin edges beyond protruding bone. Culture still positive. Serum every other day for two more doses. Dichloramine T dressings and traction continued to March 26, when culture was negative. Revision of stump, retraction of muscle and skin 2 inches bone cut off. Sinus packed with iodoform gauze. 3/31/34, temp. 100°–103°. Adenitis in Scarpa's triangle. 4/18/34, pus pocket evacuated in stump. Thereafter stump healed more promptly. 5/5/34, discharged home. It was thought that infection of stump after revision was due to streptococci and staphylococci, both of which were cultured from wound.

Since submitting this review of fifteen cases of gas gangrene for publication, two more cases have been observed at Knickerbocker Hospital and are herewith reported.

CASE XVI.—Female, white, fifty-four. Admitted August 31, 1934. Tetanus antitoxin on admission. Struck by automobile, brought to hospital in severe shock, with a complete sleeve-like avulsion of the skin and subcutaneous tissues of the left arm from shoulder girdle to hand, exposing muscles. Small tear of flexor group in forearm, radial pulse good. The wound was not grossly dirty. Immediate débridement, replacement and loose suture of skin at shoulder with several rubber dam drains—wet dressing. For thirty-six hours normal temperature and pulse, then rising abruptly to 104° and 136° F., respectively. Characteristic odor of gas bacillus infection present but no gas, no crepitation, no bronzing of skin. After consultation, guillotine amputation (Doctor Bohrer) one inch below shoulder joint—where muscle bled readily and had normal color and contractility. Amputation forty-two hours after accident. Culture of amputated arm positive for *C. welchii*. Typical muscle changes had taken place starting at point of laceration of flexor muscles, and spreading upward and downward. Patient promptly developed pneumonia postoperatively and a septic wound not in any way characteristic of gas bacillus infection and died on sixth day after admission. Transfusion and serum were not employed, but from the rapid course and the development of pneumonia and sepsis, it is doubtful if they would have been of any avail.

CASE XVII.—Male, white, twenty-two years. Admitted 10/2/34. Fell through glass door sustaining deep transverse laceration, dorsal surface, right forearm. Had severe hemorrhage, controlled by rag tied around arm. In shock on admission. Tetanus antitoxin immediately. Bellies of flexor muscles divided two inches below bend of elbow, radial and ulnar arteries severed, radial, ulnar and median nerves divided. Immediate débridement (Doctor O'Connell). Hemostasis, repair of nerves and muscles. Suture

of wound with drainage. 10/3/34, temperature rose to 104.8°, pulse 144, severe pain in region of wound, characteristic odor, no gas or crepitation was noted at any time and could not be demonstrated by roentgen ray, but marked edema extending from hand to shoulder girdle. Sutures removed—dakinization of wound. 10/4/34, condition remained same. Polyvalent gas bacillus antitoxin intravenously. Base of wound now distinctly necrotic, slight bronzing of skin, edema particularly marked in fascial planes on posterior aspect of arm. 10/5/34, smear and culture positive for *C. welchii*. Modified guillotine amputation (Dr. O'Connell) slightly above junction of middle and upper thirds of humerus—where muscle was normal in color and contractility and bled readily. Peroxide dressing to stump.

Patient had in all six intravenous injections of polyvalent serum, two on day of operation. No transfusion was necessary. After amputation, temperature fell by lysis to normal on the fourth day and recovery was rapid. Nevertheless, culture of the stump, taken every third day, continued positive for *C. welchii*. No other organism isolated. Patient discharged on twentieth day after admission. Healing occurred without secondary revision of stump.

Comment.—These two added cases are very exceptional in that gas in the discharge and crepitation were both absent although the characteristic odor, muscle changes and positive smear and culture were present. Early prophylactic administration of antitoxin might have decreased the virulence of the toxemia in Case XVI, although it is doubtful in the presence of pneumonia and sepsis, if this patient would have survived. In Case XVII, unquestionably the serum lessened the toxemia and was an important adjuvant in bringing about recovery.

Tabulation of Cases as to Type

	Local	Local Spreading	"Group"	Massive	Fulminating
Cases					
I		X			
II				X	
III				X	
IV		X-D			
V			X		
VI	X				
VII				X	
VIII			X		
IX	X				
X	X				
XI			X		
XII					X-D
XIII				X-D	
XIV				X	
XV				X	
15	3	2	3	6	1

D = Death. X = Present.

Case IV also showed definite manifestations of septicemia due to a mixed infection though blood culture remained negative throughout. No metastatic cases were encountered.

The mortality in this series was 20 per cent. It is usually between 20–50 per cent. It is worthy of note that in each instance an extremity, and not the trunk, was involved. In the latter location the prognosis is less favorable, for the impossibility of amputation predisposes to the rapid extension of the infection. The cases that died were either of the fulminating type as Case XII, the massive type as Case XIII, or the spreading type with septicemia as in Case IV. In Case XII shock and hemorrhage were contributing causes, and it is not surprising that the infection proved overwhelming. In Case XIII insidious in onset, an earlier amputation might have averted the fatality. Recovery might also have occurred in Case IV if amputation and antitoxin had been used.

The cause of the initial trauma in these cases included both severe (automobile accidents) and mild injuries, such as incised wounds, while an equal number were due to cuts with glass. In Case XIII gas gangrene followed the injection of varicose veins, for varicose ulcers, a rare complication of that condition. Manson has reported two cases of gas gangrene developing in the stump after amputation of the leg for intractable ulceration and subsequently found that the *C. welchii* was found in a surprisingly large number of varicose ulcers.

The lower extremity was affected in 80 per cent, in 20 per cent the upper. The period of invasion after trauma was one to four days, usually twenty-four to forty-eight hours. Odor of a characteristic nature was noted in twelve cases, and was probably present in the other three, although no note was made. Pain, of an excessive character, out of proportion to the local condition, occurred in eleven cases, while gas in the discharge and the characteristic crepitus on palpation were present in all but one. Although early roentgen rays were taken in more than half of these cases, gas was found only in Case XIV. It was helpful in establishing the diagnosis. At operation, typical findings of muscle changes were noted in fourteen cases. In general, the character of these changes varied according to the virulency of the invading organisms, to the extent of crushed muscle tissue, and to the destruction of the main or collateral circulation of the part involved. The so-called "mahogany red" or "boiled ham" appearance of the affected muscles, the absence of bleeding from the divided surface and their failure to contract on transverse section, are typical of this condition in neglected cases. Later necrosis with varying shades of greenish-gray or black are seen, as well as abundant gas in a foul-smelling, dirty brownish, irritating discharge. Case IX, in which no typical muscle changes were observed, was the mildest of the series. There was only a brownish discharge around the margin of a traumatic ulcer, with a necrotic base, in which *C. welchii* was found in smear and culture.

Anemia is, by far, the most common associated sympton of this disease, and to illustrate, a complete graph of Case XIV is given showing the curves of hemoglobin and red blood cell count (Graph 1). It was only marked in one other case, although no doubt present in greater or less degree in all

Tabulation of Fifteen Cases of Gas Gangrene

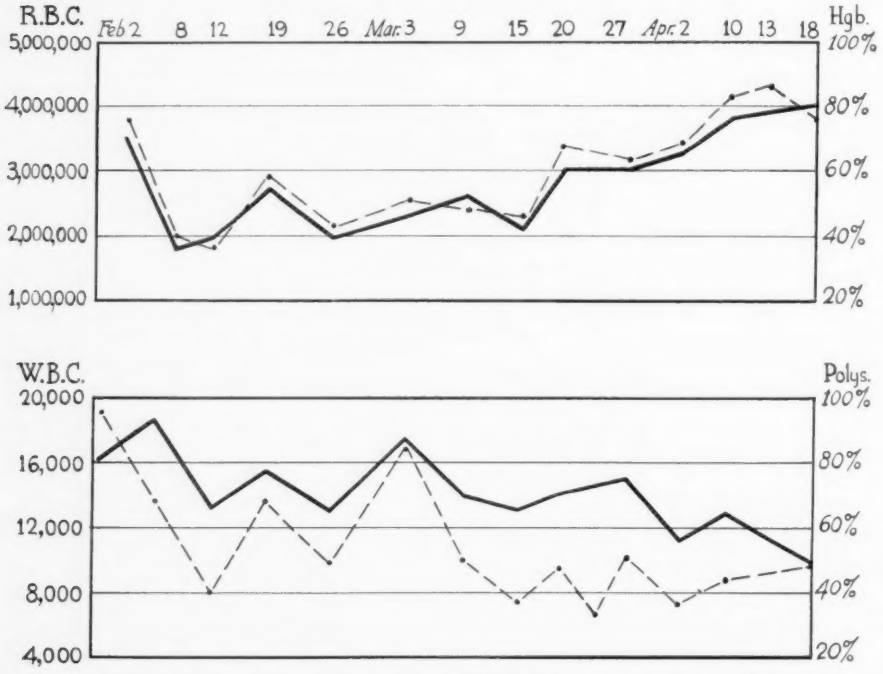
Cases	Organisms	Cause Trauma	Part	Period of Invasion	Excessive Pain	Odor	Gas	Crepitus	Early Roentgen Finding	Muscle Changes	Complication	Duration	Surgical Treatment	Serum Treatment	Transfusion	Result
I	G. B.	Cut with glass	Arm	2 days	X	X	X	X	—	?	Nerve injuries	?	D	Transferred to Roosevelt Hospital	—	Recovered
II	G. B. staph. strept.	Crushed in machine	Arm	3 days	X	X	X	X	—	X	Anemia	2 wks.	A S.S.	—	400 cc.	Recovered 4 months 3 days
III	G. B.	Crushed by elevator	Foot	3 days	X	X	X	X	—	X	—	—	S C-D A R	—	—	Recovered 9 months 7 days
IV	G. B. strept. staph.	Automobile accident	Leg	4 days	X	X	X	X	—	X	Septicemia	15 days	M.I. C-D Per-O	—	—	Death in 17 days
V	G. B.	Collision, go-cart with elevator pillar	Leg	2 days	X	X	X	X	—	?	—	—	D C-D Per-O Gr.	200 cc. tetanus-perfringens	—	Recovery 1 month 21 days
VI	G. B. staph.	Collision, motorcycle with auto.	Leg	1 day	?	X	X	X	—	X	—	—	D Per-O	—	—	Recovery 5 months 26 days
VII	G. B.	Spontaneous re-fracture	Leg	1 day	X	X	X	X	—	X	—	—	M.I. Per-O A Gr. C-D	—	—	Recovery 4 months 17 days
VIII	G. B.	Fell on spike fence	Arm, hand	2 days	?	X	X	X	—	X	—	—	S Per-O M.I. R	40 units G. B. antitox. intrav. 60 u. intramus.	—	Recovery 1 month 3 days
IX	G. B.	Laceration with glass	Foot	4 days	?	?	?	—	—	—	—	—	S C-D Boric acid wet dressing	—	—	Recovery 4 days
X	G. B.	Crushed by elevator	Foot	2 days	X	?	X	X	—	X	Syphilis	Tertiary	M.I. C.D. Per-O	—	—	Recovery 4 months 22 days
XI	G. B.	Cut with glass	Leg	3 days	?	?	X	X	—	X	Pregnancy	—	S C.D. M.I. Acr.	—	—	Recovery 26 days
XII	G. B.	Subway accident, alcoholism	Leg	1 day	X	X	X	X	—	X	Shock, hemorrhage	2 days	Per-O	—	500 cc.	Death 52 hours
XIII	G. B.	Leg ulcer, varicose vein injection	Leg	4 days	X	X	X	X	—	X	Sepsis	13 days	A	40 cc. intravenously 60 cc. intramuscularly	500 cc.	Death 17 days
XIV	G. B. strept. staph.	Automobile accident, skidding	Thigh	1 day	X	X	X	X	X	X	Shock, anemia	3 days 40 days	A Di-T C-D Acr. R	10 cc. intravenously daily for 6 days	500 cc.	Recovery 4 months 2 days
XV	G. B. strept. staph.	Bursting steam boiler	Leg	2 days	X	X	X	X	—	X	Shock, anaphylaxis, pocketing in stump	4 days 24 hrs. 3 wks.	M.I. A C-D Di-T R	10 cc. twice daily intravenously for 2 days, then once daily 4 days. After 1 week interval 10 cc. every other day for 3 doses	500 cc. before amputation	Recovery 3 months 7 days

Abbreviations used in Tabulation: *Organisms.*—G. B. = *B. welchii*, Strep. = Streptococci, Staph. = Staphylococci. *Methods of Treatment.*—C. D. = Carrel-Dakin, Di-T = Dichloramin-T, Per-O = Peroxide irrigation, Acr. = Acraflavine. *Procedure.*—A = amputation, M.I. = multiple incisions, D = Débridement, S = Suture before infection set in, S.S. = Secondary suture, R = Revision of stump, Gr. = Skin graft.

X = Present. ? = Doubtful. — = Absent.

Volume 101
Number 6

cases. Shock and hemorrhage are usually antecedent to the infection and important etiologic agents in its rapid spread and increased mortality, while septicemia, also noted in one case, was undoubtedly the cause of death. Syphilis and pregnancy, present each in one case, do not seem to have influenced the picture. Anaphylaxis or severe serum reaction should be cautiously avoided. It may occur as in Case XV, even though all usual precautions are taken. In this particular case, the intracutaneous test for this condition proved more reliable than the conjunctival. After the serum has been discontinued for some days, it is probable that a renewal of intravenous injection may cause distinct reaction. Reaction may also be expected if the intravenous injection is given too rapidly.



GRAPH I.—Showing development of anemia and leukocytic reaction in Case XIV.
Explanation.—In the upper graph, the broken line represents the number of red blood cells; in the lower, the number of white blood cells, per cubic millimeter. In the upper graph, solid line represents the hemoglobin percentage, in the lower graph, the percentage of polymorphonuclears.

Treatment.—It is worthy of note that four cases herewith described had been closed by some form of suture, while débridement without suture had been done in three others. This fact merely indicates that these wounds, in which gas gangrene subsequently appeared, were considered either of the incised or contused variety and were treated accordingly. It is only in wounds in which the circulation has been impaired and soft tissues crushed, conditions in which primary union is impossible, that special precautions must be taken against the development of gas gangrene. These include painstaking hemostasis, the removal of all blood clots and foreign material,

débridement, and the making of numerous counter-openings to prevent any possible retention of discharge in the area of damaged tissue. Such measures are prophylactic against the retention of pyogenic organisms and of those of gas gangrene as well. The latter may also be inhibited by the freedom of entrance of oxygen into the tissue interstices which the numerous counter-openings permit. Careful vigilance must follow the initial treatment of the wound to detect the presence of any organism of gas gangrene in its discharge. If cultures show the Welch bacillus, the Welch antitoxin must be given without delay. If more than one variety of anaerobic organisms is present, the use of the polyvalent serum is indicated. The value of these therapeutic agents in the early stage of gas gangrene cannot be too strongly emphasized.

Further surgical measures in cases of unquestioned gas gangrene depend upon the location of the wound and the virulence of the infection. In war, infection is not infrequent on the trunk and, in this location, wide excision only of the infected area is possible. Of this type the cases herewith reported contain no example, gas gangrene of the trunk occurring but rarely in civil practice. In the extremities reference to the clinical histories shows eight cases in which the patient recovered without amputation, and of the three fatalities, all occurring in gas gangrene in the lower extremity, one died within forty-eight hours from shock and hemorrhage without amputation, one after seventeen days without amputation, and one after seventeen days subsequent to amputation, in the two latter cases sepsis being a contributing factor to the fatal issue. It is therefore obvious that amputation is not always essential and this same conclusion was reached by surgeons in the world war. In both civil and war conditions, however, amputation is imperative when the circulation of the extremity is so impaired that it is no longer viable.

Amputation is also usually indicated when the period of incubation does not exceed twenty-four to forty-eight hours and when, after an invasion decidedly acute, symptoms of oedema and crepitation quickly develop and extend toward the trunk. In Evacuation hospitals this type of acute case was not infrequent while, in the Base hospitals, gas gangrene not appearing until after a week or ten days, the infection was correspondingly less virulent and amputation was the exception, recovery following the local excision and drainage of the infected area. In the border-line cases, in both civil and war surgery, the question of radical treatment depends upon surgical judgment. In a previous essay on this subject, published by the Surgeon General's office in 1927, the writer (Eliot) referred to conditions on which the exercise of this surgical judgment must be based. It is there stated that amputation is ordinarily indicated in extreme laceration of soft parts, in the involvement by the infection of several groups of muscles, in the presence of extensive comminution of bone with or without opening into a large joint, where gangrene is self-evident, and where symptoms of toxaemia develop early. It is also indicated when the infection shows a tendency to

extend rapidly toward the trunk. On the other hand, conservative measures are justifiable when the period of incubation has been relatively long, when the infection involves the distal part of an extremity, when it is localized or very slowly extending, where the main circulatory channels are intact, where no fracture exists and where no large joint has been opened.

The question of the time of amputation has been referred to. It should invariably follow promptly the decision that the sacrifice of the extremity is necessary. The plane and type of amputation are important. The plane should be well above the infected area, especially the involved muscle tissue and the contiguous oedema in the fascial planes where gas bacilli are found in large numbers. It is also well, if possible, to divide the soft tissues on the proximal side of any demonstrable crepitation. This cannot always be done, however, and it is of interest to note that in Case XV a limited area of crepitation persisted for almost a week after amputation of the thigh slightly below the outer part of Poupart's ligament. During the war, the so called guillotine amputation, in which theoretically all soft tissues and the bone are divided in the same plane, enjoyed a certain vogue. It has the advantage of speed but the disadvantage of usually requiring some weeks later, a secondary revision of the muscle planes and bone to permit the covering of the stump with skin. This was necessary in Cases XIV and XV and it is of interest to note that the revision was not undertaken until culture of the discharge from the granulating stump showed an absence of gas bacilli. It was then carried out without any recrudescence of the original infection.

As a substitute for the guillotine method, a flap of skin and subcutaneous tissue can be easily and quickly turned back a distance of several inches permitting the circular division of muscle tissue and that of the bone at a still higher plane, which can be done as quickly as the guillotine amputation. The stump so fashioned may be compared roughly to a cone of which the divided bone forms the apex, the edge of the flap, the circumference of the base, and the divided muscle tissue, the side. The cuff of flap tissue is allowed to remain in place, the denuded muscle and bone draining freely for from thirty-six to forty-eight hours, when the cuff is turned down and ultimately closes the extremity of the stump. The crease at the base of the reflected cuff must be carefully watched and any tendency to constriction relieved by immediately releasing the cuff. Ultimately, healing by granulation follows and no secondary revision is necessary.

In the absence of amputation, multiple incisions, with the excision of necrotic muscle, which is the unquestioned culture medium of the specific bacillus and which therefore favors its propagation, must be carried out. Carrel-Dakin solution is applied continuously to all denuded tissue, or dichloramine gauze—a modified Dakin agent—which insures relatively painless dressings, is employed. Peroxide of hydrogen and weak solutions of sulphate of quinine have also given good results. It is most important to avoid

any pressure on the infected area or its immediate vicinity, and thereby the expression of agents of infection into uninvolved tissue.

The local treatment of the wound, with or without amputation, must be supplemented by measures to support the general condition of the patient and to combat the effects of the infection. Although of doubtful value, as in sepsis in general, transfusions of small amounts (300 cc.) especially in the early stages of the infection may alleviate that condition. Of considerable value are transfusions in larger amounts (500 cc.) for the relief of the associated shock, hemorrhage and anemia. Repeated injections of the appropriate serum inhibit the extension of the infection to distant parts of the body. Reference to the table shows that in Cases XI and XIV transfusion was of benefit in relieving the anemia. Transfusion at no time contraindicates the use of saline infusion, hypodermoclysis, or enteroclysis.

In conclusion, the importance of prompt and energetic treatment cannot be unduly emphasized. In war the prognosis is more serious, for there is frequently delay in the succor of the wounded, with associated shock and hemorrhage, while in civil life patients, shortly after the accident, are taken to well equipped hospitals where they receive both adequate surgical treatment and the immediate injection of antitoxin as soon as the infectious organism appears in the discharge from the wound. In no case should this injection be delayed until crepitation develops. The advantage of the early use of this remedy in wounds of the trunk is quite obvious. While the results of antitoxin therapy in the World War were not especially encouraging, its use in civil surgery has hitherto proved much more satisfactory, due perhaps (although this requires further investigation) to the prevalence of infection by the Welch bacillus alone, while during the war (at least on the Western front) several different anaerobic organisms were frequently present in the same wound. So encouraging, in fact, has the use of antitoxin proved in the limited number of cases herewith reported that, as in the case of tetanus, this valuable agent ought to be made available by Health Boards of Urban Centers.

SYMPOSIUM

ON

CARCINOMA OF THE BLADDER

AT

THE FIFTIETH ANNIVERSARY OF THE MEMORIAL HOSPITAL

NEW YORK, N. Y., MAY 25, 1934

Chairman, BENJAMIN S. BARRINGER, M.D.

CARCINOMA OF THE BLADDER. C. RUTHERFORD O'CROWLEY, M.D., Newark, N. J.

SURGERY OF BLADDER TUMORS. EDWIN BEER, M.D., New York, N. Y.

CYSTECTOMY FOR CANCER OF THE BLADDER. WILLIAM C. QUINBY, M.D., Boston, Mass.

DIATHERMY FOR CARCINOMA OF THE BLADDER. VIRGIL S. COUNSELLER, M.D., and WILLIAM F. BRAASCH, M.D., Rochester, Minn.

RADIUM IN TREATMENT OF CANCER OF THE BLADDER. BENJAMIN S. BARRINGER, M.D., New York, N. Y.

TREATMENT OF BLADDER CANCERS WITH EXTERNAL IRRADIATION. ARCHIE L. DEAN, M.D., New York, N. Y.

FATE OF UPPER URINARY TRACT IN CARCINOMA OF BLADDER. JOHN R. CAULK, M.D., St. Louis, Mo.

FOREWORD

THIS conference is an attempt to obtain the many points of view of surgeons whose experience in this field qualifies them to speak authoritatively on the different intricate problems involved in the diagnosis and treatment of bladder carcinoma. Notwithstanding the natural difference of opinion as to the proper treatment of this disease, explanations for some of these divergent opinions were suggested. It is hoped that these articles will result in a closer study of the various problems presented and a more intelligent understanding of the reasons for the varying points of view, resulting in the limiting of certain types of bladder carcinoma to certain forms of treatment.

CARCINOMA OF THE BLADDER

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All epithelial cells are soft and plastic, being able to adjust themselves to influences which increase or decrease the general surface area. This is especially striking in the stratified squamous, so called transitional, epithelium of the urinary passages and bladder where they are under the influence of rapid alterations in size and shape. Beneath the superficial cells are several layers of polygonal cells, while upon the basement membrane is the usual single layer of small cuboidal cells. The stroma consists of fine loosely arranged connective tissue containing many lymphoid cells and sometimes lymphoid nodules. Beneath this is the less cellular submucosa. Small glands resembling those in the prostate and termed "aberrant prostatic glands" are found in the urethra and in the female urinary bladder. Those structures which were formerly believed to be glands are gland-like depressions composed of solid epithelium; these and the aberrant prostatic glands may give rise to cysts.

Bladder tumors are particularly interesting, (1) because of the remarkably indefinite line of demarcation which exists between relatively benign and the more malignant growths and (2) because of the apparent tendency to implantation. It may be stated in passing, that no field of microscopic diagnosis gives less satisfaction to the microscopist than the subject of bladder tumors, although, as we will show later, in only about 5 per cent of the cases are there slight errors in the grading of tumors made at the time of biopsy that are ultimately corrected when surgical removal of the tumors is done. Because of the question raised by Broders, from whom I will subsequently quote, many pathologists object to calling papilloma of the bladder which shows no atypical cells or other evidence of malignant change, Grade one carcinoma, but prefer to set these aside as simple epithelial papillomas not to be graded. We, however, in this paper, have followed the ideas as expressed by Broders.

The suggested classifications of bladder tumors, the majority of which are epitheliomas, are at present confusing and voluminous. While there is not as yet uniform agreement in classification and grouping, the majority of authorities concur in the following opinion rendered by Doctor Broders:

> In view of the fact that the protective epithelium of the urinary bladder is of the stratified squamous variety (so called transitional), new growths that arise from the regenerative cells of this epithelium and tend to differentiate like it, are called squamous cell epitheliomas regardless of whether they are papillary, flat or infiltrating. I do not recognize benign papilloma of the bladder as an entity, but place all so called papillomas in the category of epithelium. As a whole, the nucleocytoplasmic ratio of the cells of the so called benign papillomas is larger than that found in the cells of the normal

protective epithelium of the bladder. Also the nuclei of the cells of so called benign papillomas have a tendency to irregularity in outline and show an increased avidity for the basic dyes which is not found in the normal epithelium. As a rule, the cells in a section from the tip of a frond of the so called papilloma show the same structure as those in a section taken from its base. The cells do not have to break through the basement membrane of the bladder in order to be considered cancer. The so called papillomas usually fall in Grades one and two squamous cell epithelioma, rarely in three and four.

In this paper we will follow this classification, now rather widely adopted and accepted by the Carcinoma Registry of the Urological Association. Of the 902 cases reported by this Registry, 436 were papillary carcinoma while 446 were infiltrating carcinoma, and 20 were of unusual type. 866 were graded: 20 per cent were Grade one, 33 per cent were Grade two, 35 per cent were Grade three, and 12 per cent were Grade four.

The villus of the simple papilloma has a stalk containing a thin-walled blood vessel and a variable amount of connective tissue. The papilla is covered with layers of epithelial cells in approximately the same number as the normal bladder mucosa. The rows of cells are regular and symmetrical and are apparently in a state of rest, being attached at right angles to the poorly cellular stalk. The villi in the more malignant papillary growths are similar to each other but there is polymorphism with cells heaped in thick disorderly masses and showing greater avidity for basic dyes. Even in the basal layer the cylindrical cell polarity is lost. The idea that the malignant change always first manifests itself as an epithelial invasion of the pedicle is now known to be incorrect. This change may first make itself evident in one of the fronds. Occasional solid masses of cells, some compressed on a very vascular stalk and occasional hollow epithelial lined tubes are sometimes produced similar to those found in adenocarcinoma. This suggests to one's mind the fact that the bladder epithelium arises from an anlage similar to that of the intestinal mucosa. Small cells are frequently seen in the stalk. As the carcinoma advances, extensive invasion of the bladder wall occurs and the bladder may be filled with large fungating masses. The infiltrating variety forms no projecting masses on the surface but invades the deeper tissues, giving rise to an ulcer with a raised thickened border which microscopically is a scirrhous growth with abundant fibrous tissue. Occasionally one sees plateau-like thickenings which infiltrate neighboring tissues.

Occasionally cystitis-cystica may become a glandular cystitis with the formation of tubes lined by mucus producing cylindrical epithelial cells. These cells may give rise to a single non-villous cylindrical cell carcinoma and they also may be the source of origin of mucoid or colloid carcinoma. Adenomas or fibroadenomas are unusual. They may arise from the aforementioned glands but some arise from the lower cylindrical cells of the deeper layers of the epithelium. Myxomas, fibromyxomas, leiomyomas and fibromyomas are rare; rhabdomyomas also occur. Sarcomas are rare, occurring more frequently in women, in childhood and at puberty; these partake of the nature of round, spindle cell or myxosarcomas. Dermoids are rare.

Secondary involvement of the bladder by growths arising in neighboring organs is relatively frequent but the reverse is unusual; these result in fistulae.

Gross Pathology.—From observations made on dye workers it is suggestive at least that in malignancy occurring in these individuals that the bladder tumor originates in the basal layer of epithelium about the terminal blood vessels and may reach considerable size before the superficial layers of epithelium become involved. The distribution of tumors usually follows the vascular supply in deeper layers. Occurrence of multiple tumors may be accounted for in this way. It is suggested from the work of Pachikis and Bengel that bladder carcinoma shows the same early changes in the epithelium that has been observed in aniline cases.

Position.—The location of 854 tumors of bladder reported to the Registry, involving adjacent or multiple areas, was as follows: Trigone 32.2 per cent, lateral walls 35.3 per cent, bladder neck 9 per cent, posterior wall 10.2 per cent, vault 7.5 per cent, anterior wall 5.7 per cent. Of these 854 cases, in 473 only was one area of the bladder alone involved. This, of course, gives a better idea as to the frequency of location. They were located as follows: Trigone 27.37 per cent, lateral walls 41.89 per cent, bladder neck 5.89 per cent, posterior wall 10.92 per cent, vault 7.58 per cent, anterior wall 6.32 per cent.

In view of the fact that those tumors on the lateral walls usually involve the ureteral orifices, it can be seen that these tumors located in this region with those on the trigone and bladder neck constitute 76.6 per cent. This, therefore, brings out clearly the fact that in only 23.4 per cent of tumors is it possible to apply complete excision without interfering with the ureter or urethra. It follows that any type of treatment which might be advocated for use with all bladder tumors must consider first the high percentage of tumors which are so located that surgical treatment becomes formidable and carries with it great risk, namely, more than three-quarters of all cases. Of 36 tumors which involved only the vault, 75 per cent were of Grades three and four. Because of the high degree of malignancy in the vault and because of lack of intervention of nodes along the course of the obliterated hypogastric vessels in their course to the liver, there is a higher frequency of metastases in this area than of tumors in any other position in the bladder. Of tumors elsewhere, in the bladder, 53.4 per cent were of Grades one and two. Therefore it will readily be seen that these latter have an equal chance of falling in a lower group while with tumors of the vault there is a 75 per cent chance of high malignancy. With the exception of tumors of the vault the location of the tumor has little to do with the prognosis.

It is obvious from statistics available, that if the tumor be multiple it is of a low grade malignancy falling in Grades one or two in three-quarters of the instances, whereas, a single tumor will fall into Grades three or four in 50 per cent of the instances. This accounts for the fact that multiple tumors

run a peculiar course often extending over many years. There is a case reported followed for 60 years. But in spite of this fact it is evident that multiple tumors are often malignant, no matter how low the grading. It has been shown that in these prolonged cases there is no recurrence in properly treated areas but that the new tumors are new growths. There are also several cases of record where even though no subsequent new growth has made its appearance after removal of a microscopically benign tumor that metastases and infiltration of neighboring organs has occurred.

Ten per cent of the carefully studied and autopsied cases in the Registry showed metastases in the following degree of frequency: (1) bones, (2) lungs, (3) regional nodes, (4) liver, (5) retroperitoneal nodes. Wound implantations I believe were extremely rare; in this series of 902 cases, there were none reported.

Regardless of the Grade of the tumor, the percentage of recurrence varies little and followed the initial treatment in 46.2 per cent of cases. Multiple tumors are more prone to recur than single. This, however, is probably due to the growth of new tumors. This suggests that possibly new growth of the bladder is a diffuse disease of the bladder mucosa or possibly a general circulating cancerogenic substance.

Size.—The size of the tumor bears a definite relationship to the prognosis. It is seen that of 48 small tumors, *i.e.,* ranging from 1.9 cm. to 2.4 cm., 54.2 per cent were alive at the end of five years. Of 91 medium sized tumors between 2.4 cm.–4.9 cm., 39 per cent were alive in five years; whereas, of 155 tumors larger than 5 cm., 25 per cent were alive in five years.

There were not enough cases in the Cancer Registry to make even a close approximate value of various types of treatment.

Attempting to evaluate the general mortality of carcinoma of the bladder of all types from the literature of the past 20 years is a fairly hopeless task, because of many variables. Many cases are reported before even the three-year period has elapsed. These are deleted from the statistics entirely. Many cases have not been evaluated either by biopsy or specimen and many reporters report on general mortality of bladder tumors, a large percentage of which tumors, of course, are simple papillomata. Many, however, do not include these cases.

Of 2,597 proven cases of papillary carcinoma, two types were usually recorded by observers corresponding to Broders' classification, *viz.,* (1) papillary, (2) infiltrating carcinoma. Of these 2,600 cases 66 per cent or two-thirds were dead within three years. Since we are considering only cases either dead or living at the end of three years, this is a fair idea of the mortality. Of the papillary type, mortality was 48 per cent, whereas, of the infiltrating, it was 78 per cent in three years.

As to Grade mortality in the Registry cases, 71 cases of Grade one tumors had a mortality of 33 per cent in five years. Of 82 cases of Grade two, the mortality was 60 per cent. Of Grade three, 120 cases mortality was 80 per

cent and Grade four, 42 cases 95.5 per cent mortality in the five-year period.

In attempting to compare statistics from different clinics, we again become confused. Some clinics record only operative cases, and report only 50 per cent of the cases seen as operable. The same is true for results obtained from radium treatment, as in many instances radium was only used as a palliative measure in hopeless cases.

There are 339 cases described in the Carcinoma Registry either living or dead at the end of the five-year period. Of these only 102 are living over five years.

In the total number of cases the poorest results seem to have been obtained by scalpel resection or excision. The total estimated mortality on all cases thus treated is 85 per cent as compared to a general mortality of 66 per cent. Excision or resection cannot be the operation of choice, due, of course, to the inaccessibility of many tumors.

Fulguration by the actual cautery has advantages over resection but is not nearly so effective as the cold cautery plus the radio knife. In these statistics a combination of fulguration and excision in 287 cases had a mortality of 52 per cent in three years as compared to general mortality of 66 per cent. Of course, these cases were much more favorable ones than the cases in which radium was used. In many instances operators observe that the cases had progressed too far for fulguration and radium was implanted. We can conclude, however, that the general run of carcinoma of the bladder coming to a urologist can exact a three-year cure in nearly one-half of the instances by this method which is certainly more effective than resection.

Barringer reported in 1930 control of 48 of 127 cases of advanced carcinoma of the bladder. These were controlled over three years, a mortality of 62 per cent, an even lower percentage in these very advanced cases than the general mortality of all cases.

Appendage to Treatment.—It is the consensus of opinion of urologists that roentgen ray therapy is valuable in two instances: (*a*) For control of symptoms after operation, and (*b*) for inhibition of the growth of new tumors of low grading after operation. Unfortunately statistics are of little use in evaluating this. The mortality of the 2,597 cases treated in all manners prior to the Registry cases was 66 per cent in three years. The mortality of the Registry cases was 66 per cent in five years—suggesting an improvement in results.

The trend in the future will be more and more (*a*) in surgery to adopt more radical procedures. The complete cystectomy operative mortality has averaged 27 per cent and theoretically the remaining 73 per cent of cases should have a 90 per cent chance of cure, deleting the 10 per cent of cases which metastasize. This would mean about 65 per cent of cures in cases so treated but, of course, such results are improbable due to ascending renal infection and other complications. We have only record of 18 such cases, not enough for comparative statistics. (*b*) By improved methods of radium implantation and increased dosage.

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SURGERY OF BLADDER TUMORS

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BEFORE discussing the standpoint that we have reached in the surgery of bladder tumors, I want to make some general remarks on the subject of the problem involved. It is going to be difficult to come to any agreement as to therapy until surgeons are ready to become more open-minded and willing to try all methods, and to equip themselves to carry out all approved procedures, using the same nomenclature in interpreting their cases. A narrow viewpoint has added to confusion in this field, and we all know that for years there has been a good deal of confusion in the pathology, biology and therapy of bladder tumors. There has been a great urge to dogmatize on the basis of Hansemann's anaplasia theory, and some clinics still firmly believe that they can group and grade biopsy specimens removed through the cystoscope with great accuracy. They believe that one part of the growth is typical of all the growth, despite the fact that everybody of experience has occasionally seen in one slide of a series of sections a typical benign palisade and in an adjacent section, or even in parts of the same section, definite cell atypism and stroma invasion. Only recently the Wilmington group showed us a slide characteristic of this condition, which I was shown 31 years ago while making serial sections of bladder papillary growths in the laboratory of H. Chiari in Prague. Mandelbaum and Aschner have reproduced photomicrographs of sections of papillary tumors showing this same phenomenon. Bladder growths lend themselves to grouping in three clinical and pathologic classes, as I see them: first, benign papilloma; second, papillary carcinoma; third, solid infiltrating carcinoma, often squamous celled in type. To attempt a further subdivision, based on microscopic data, I believe makes for confusion.

Further confusion is created by the pathologist, as well as by the surgeon, in his interpretation of infiltrating characteristics. Tumors may be superficial and show infiltration of the stalk or even of the pedicle. These naturally can be approached with some success by electrocoagulation, or radium. In the infiltrating group, I place those growths that invade the bladder wall, can frequently be felt by rectum or vagina before operation, and feel on the operating table like a solid, more or less nodular plaque in the bladder wall, after thorough extraperitonealization of the organ. Both groups appear as infiltrating in the literature—in the former, results with any therapy are fair; in the latter, no therapy but resection and wide resection or total cystectomy will give adequate results. Through the open bladder, the palpating finger may readily be mistaken, so that one thinks one is treating such a diffuse infiltration and one reads of reports of such cases cured by electrocoagulation and radium, which may be more or less misleading. Seeding with radium or coagulating the really solid, infiltrating growths is a hit-or-miss procedure,

to my mind, but on occasion may be the best we can do, and may occasionally succeed. The calling of benign papillomata as "Group I Carcinomata," and the publishing as infiltrating carcinomata cases in which the involvement is superficial, make for real confusion in the interpretation of results. Again, further confusion is caused by what seems to be the variety of the material observed in the various clinics. Recently at The Mayo Clinic I was told that autopsy showed metastases in bladder tumors in about 30 per cent of the cases, and about half of these were visceral. Smith reported from the Massachusetts General Hospital an even higher percentage of metastases. On the other hand, in our material the total autopsy figures being smaller, about 10 per cent only showed metastases and visceral metastases were not observed. Further confusion is caused by the fact that multiple tumors may be present in the bladder, some benign and others malign, some malignant papillary carcinoma and others obviously infiltrating the bladder musculature. If we excise the latter and use electrocoagulation and radium on the former, as we have often done, where both sides of the bladder, or one side of the bladder and the neck were involved, should recurrence develop, how can we apportion the responsibility? That which has been excised surgically is in a fixative and cannot be held responsible.

Again, in studying results, further confusion develops from the peculiar biologic characteristics of these growths. Some papillomata after destruction recur locally or in different parts after complete, well-controlled destruction. Other cases develop papillary carcinomata or even solid gowths years after the destruction of the original growth or growths. Some patients after excision or control of solid carcinomata come back with benign recurrences, though, unfortunately, too frequently with malignancies, which are not truly recurrences, but are overlooked or left in parts of the original tumor. I fear that until we get some insight into the causative irritant, these peculiar biologic elements will continue to confuse us, and it will prove upsetting to our statistics because of the difficulty of differentiating between new tumor formation and real recurrences or incomplete removal.

As a result of the above conditions, we can readily be led astray in estimating the value of our therapeutic efforts, and I come back to my original thesis, that if one has adequate material one should be equipped to apply all types of therapeutic methods and not become too dogmatic and blind oneself to other methods and the possibility of misinterpreting what one has treated, and of one's end-results. Of only two things do I feel fairly sure: benign papillomata can be destroyed and cured transurethrally (or suprapubically) with the high frequency currents; papillary carcinomata, infiltrating the bladder wall deeply, and solid infiltrating carcinoma can be completely and regularly removed only by total cystectomy. Partial cystectomy, the more extensive the better, usually with the sacrifice of the ureter and neostomy, gives a fair result (40 per cent for three years) in our hands in infiltrating, papillary carcinoma, whereas in the solid infiltrating growths, although partial

cystectomy has given cures, still these cases present our biggest problem. In both these groups, we have used radium extensively, with higher mortality than following the partial cystectomy, and only an occasional cure in cases deeply infiltrating, after considerable, prolonged suffering.

It is evident from our extensive experience that the chance of cure, whatever the therapy applied, will be directly proportionate to the depth of infiltration and the size of the tumor, rather than the microscopic grading. Superficial, infiltrating, epithelial growths give about the same results following electrocoagulation and partial cystectomy, as do the cases of multiple benign papillomata treated by suprapubic cystotomy and electrocoagulation. Deeply infiltrating solid growths are rarely cured, except by wide excision or total cystectomy, and the chances of cure are better by the latter procedure.

Transurethral radium implantation in small superficial papillary carcinoma has given us a fair number of satisfactory results, combined with electrocoagulation. In those cases of persistent recurring benign papillomata deep roentgen ray seems at times to have assisted the electrocoagulation therapy.

Finally, lack of adequate control of patients by cystoscopy for one reason or another and the advanced age at which many cases begin treatment interferes with a clear-cut statistical study of the results of the various types of therapy employed over a long postoperative period.

Many of the above factors force the surgeon to adopt an attitude of trial and error, and having made use of all methods of approach which are well known to this audience and which I have repeatedly described in detail, he must adhere carefully to what has appeared to be the best.

In conclusion I might say that during recent years a great many methods of approach have been developed in the treatment of bladder tumors. This is a natural evolution, based upon the great variety and disposition of these tumors. From what has been said, it must be evident that varying methods of therapy will be indicated, depending upon the position, the number and the character of the tumors. One cannot be dogmatic in this field, and limit oneself to one method of approach in all bladder tumors. One must be prepared to apply a great variety of methods, depending upon one's own experiences and the experiences of others.

There are available in the treatment of bladder tumors the following procedures:

(1) Transurethral electrocoagulation with the bipolar or monopolar current.
(2) Transurethral introduction of radium emanation seeds.
(3) Deep roentgen ray therapy.
(4) Suprapubic cystotomy:
    (A) with electrocoagulation of the tumor and its base;
    (B) with electrocoagulation or excision, combined with implantation of radium emanation seeds.
(5) Suprapubic, extraperitoneal resection of the involved bladder wall:
    (A) with transplantation of the ureter;
    (B) with ligation of the ureter.

(6) Various combinations of the above in multiple tumors; resection of the main tumor and electrocoagulation or radium implantation in secondary or smaller tumors.

(7) Suprapubic, total cystectomy and partial prostatectomy for infiltrating malignancies at the neck of the bladder:

(A) with transplantation of the ureters into the skin of the iliac region;

(B) with transplantation of the ureters into the colon.

With these various methods available, in each case the operator must decide either from the cystoscopic picture or from data obtained during the operation, just which method he thinks the most suitable for the individual case.

TOTAL CYSTECTOMY FOR CANCER OF THE BLADDER

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IT IS a most unfortunate fact that malignant neoplasms of the urinary bladder show a marked tendency to be situated in the base of this organ. In a recent study at the Registry for Carcinoma of the Bladder[1] of 902 cases of bladder tumors over 75 per cent were found to take origin either on the trigone, bladder neck, or low lateral wall. This of course means that less than one-quarter of all the bladder carcinomata is accessible to surgical removal without interference with the ureteral insertion or the vesical sphincter. It is to this fact as well as to delay in diagnosis that the deplorable results in our treatment of this most distressing form of malignant disease are due. The present communication will consider only treatment of bladder carcinoma by total cystectomy together with uretero-intestinal anastomosis.

The operative removal of the urinary bladder inevitably includes the problem of the diversion of the urine—and it is the perplexity of this latter factor which has led the surgeon in many instances to content himself in his treatment of cancer of the bladder with measures which are much less thorough and radical than are those which he brings to bear on malignancy situated in other organs or regions of the body. Though the bladder itself may be removed with but little more difficulty than is the lip or the tongue or the breast, one hesitates to adopt such a measure when doubt remains as to the future fate of the kidneys.

There are three possible methods of disposal of the urine after the bladder has been removed: either it may be delivered directly onto the loin through a nephrostomy or pyelostomy wound; or each ureter may be brought out onto the adbominal wall in the inguinal or lateral regions; or the ureters may be implanted into the intestine. The drawback of each of the first two methods is the inevitable early and serious infection of the kidneys, besides the necessity of some sort of apparatus to collect the urine with all its attendant discomfort and complicated care. The dangers of the third method—

that of uretero-intestinal anastomosis—are the risk of immediate operative infection resulting in peritonitis, and later renal involvement from obstruction to the flow of urine away from the kidney, or infection, or both. After the first two types of disposal of the urine, the patient leads an uncomfortable, miserable existence, constantly surrounded by the odor of decomposed urine. The third operative method leaves a patient entirely comfortable, the rectum acting splendidly as a urinary receptacle.

Although transplantations of the ureters into the bowel were undertaken as early as 1851 for exstrophy of the bladder (Sir John Simon) no real success followed such attempts until the operations of Stiles in 1907. These in turn were followed by the brilliant work of C. H. Mayo and somewhat later of Coffey. The idea at the basis of all of Coffey's work has been to reproduce in the intestinal wall as nearly as possible the normal valve-like arrangement by which the ureter enters the bladder wall. This is accomplished by an oblique insertion of the ureter through the wall of the gut instead of a direct implantation used by earlier surgeons. As a result of these observations, together with the extensive operative experience of Mayo, the operation which substitutes the intestine for the urinary bladder has now come to be rather widely employed and, I think, may be said fairly to have become standardized as concerns its general technic. Certainly uretero-intestinal anastomosis is no longer an operation attended by so great a risk as to be only a method of last resort.

The above statements are borne out by the study of the end-results of such anastomoses when they have been applied to cases of exstrophy of the bladder in which cases there is no malignant factor to complicate the clinical picture and for which ailment this operation is acknowledged today to be the best form of treatment. A study of this nature is at hand in the report of Walters[2] from The Mayo Clinic. He finds that "Of 76 patients operated on, three died in hospital subsequent to operation, 27 patients have lived five years since operation, and 13 have lived ten years. The result was unsatisfactory in only three cases. In 50 per cent of the cases there was no evidence of renal infection. In 20 per cent there were short periods of mild renal infection; the interval between such periods in most cases was many months, sometimes years. Study of these patients by pyelography leads to the belief that the renal function is normal and that there is no dilatation of the pelvis, calices or ureters in cases in which the uretero-sigmoidal anastomosis is accurately carried out." Certainly results such as these will justify employing this form of relief for the patient suffering from cancer of the bladder in all instances in which removal of the entire bladder is indicated.

A consideration of the end-result statistics of all forms of treatment of bladder cancer finds them to be so much inferior to those following treatment of other forms of malignancy as to be really deplorable. In many instances this is without doubt due to tardiness of diagnosis. In others, however, the fault must be placed frankly on inadequate or timorous methods of attack

by the surgeon. Variations in the degree of malignancy of the individual tumor also play a part.

At the Urologic Clinic of the Brigham Hospital it has not seemed wise to apply one single form of treatment to the problem of cancer of the bladder but, in so far as possible, to treat each instance of this disease either by excision or radium or partial or complete cystectomy as seemed most applicable and likely to give the best result.

Of those cases in which total cystectomy has been done their operability by this method has been judged on the basis of four criteria. First, the carcinoma must be found to be situated not only in the bladder base, its fixed portion, where in fact it is most often, but the growth must be in such close proximity to the vesical sphincter that removal by any method must result in incontinence. The second criterion of operability has been that there shall be no demonstrable metastases of the tumor to the regional lymph nodes, or to those at the aortic bifurcation. Cystectomy has not been performed in any case in which preliminary laparotomy has shown such extravesical progression of the malignancy. The third element has been normal renal function, certainly of one kidney, preferably of both, as demonstrated by ureteral catheter. The fourth consideration has been the demonstration of actively growing carcinoma on examination by micrscope. All patients are first studied by cystoscopy and by roentgen ray of chest and skeleton to exclude metastases. The renal function is estimated and pyelograms made, retrograde if possible, if not by the intravenous method. At the first operation the area of lymph drainage away from the bladder is investigated, and if no secondary deposits of malignancy can be determined, anastomosis of a single ureter is performed. Following recovery from this operation, the second ureter is transplanted and the bladder, together with the prostate in the male or the whole urethra in the female, is excised. The electrosurgical needle is of great advantage in the conduct of both the anastomoses as well as in the excision of the bladder.

Ten patients to date have been treated in the above manner. Two are alive: one, a woman, at three years without evident recurrence; one, a man, at eight years with known recurrence about the rectum and prostate during the past year. Of the remaining eight patients two of the earlier cases died as a direct result of operation, which was imperfect in one way or another. The remaining six patients have died of recurrent cancer at longer or shorter periods after operation. In none of these, however, was there any further acute difficulty on the part of the urinary tract.

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DIATHERMY FOR CARCINOMA OF THE BLADDER

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Two avenues of approach are available in treatment of carcinoma of the urinary bladder: namely, the transurethral and the suprapubic routes. When the tumor is comparatively small and the degree of malignancy is graded one or two, it has been the practice at The Mayo Clinic to destroy the growth by transurethral electrocoagulation. However, with recent improvement in transurethral procedures, small, papillary lesions graded three or four, that are easily discerned and present no clinical evidence of having infiltrated the wall of the bladder, have been treated in the same way. This method may be combined with transurethral implantation of radon seeds. If such lesions can be treated successfully by this method it is of distinct advantage, since the operative risk and morbidity are much less. It should be stated, however, that unless electrocoagulation is as extensive and thorough as the coagulation would be if done by suprapubic diathermy, the procedure is worse than useless.

The more extensive, highly malignant lesions and the widespread lesions of low degrees of malignancy are attacked by the suprapubic route, using segmental resection, with disposition of the ureter when it is involved, wide excision, electrocoagulation, insertion of radon seeds or needles containing radium, and, in some cases, a combination of these procedures.

The decision as to the method of approach to these tumors is extremely important. It is governed by the type of lesion, considering whether it is small and pedunculated, or flat and ulcerated, its situation with respect to the trigone, ureteral meatus, lateral walls and dome, the grade of malignancy and the ability of the cystoscopist to discern the lesion completely. The small, flat, ulcerating lesion of Grades two, three, or four usually should be reached by suprapubic transvesical approach, on account of the tendency of a lesion of this sort to infiltrate the wall of the bladder and to spread out beneath the mucosa.

In the surgical treatment of carcinoma of the bladder it has been the custom at The Mayo Clinic, for many years, to remove the lesion by segmental resection or excision whenever either can be done. Analysis of the results justifies continuation of this procedure until some other method has been proven to be superior. Complete surgical removal of carcinoma of the bladder, whenever possible, is therefore the procedure of choice, but unfortunately a high percentage of these tumors involve the base of the bladder, trigone, urethra and ureteral orifices, and thus are inoperable or non-resectable. Some patients present themselves for treatment so late in the course of their disease that only palliative measures, if any, are advisable. Hunt[5]

estimated conservatively that, excepting lesions amenable to transurethral treatment, not less than 25 per cent of the major malignant lesions of the bladder are inoperable. Until patients learn to seek treatment early, more attention must be directed to eradicating those lesions that are confined to the base and neck of the bladder and that are considered non-resectable.

Before the introduction of diathermy, an attempt was made occasionally to destroy the large growths by the actual cautery, not so much with the hope of cure as of producing gratifying palliative results. Bumpus[1] reported 15 cases in which highly malignant lesions were treated in this manner, between January 1, 1915, and July 1, 1927; six of the patients died within a year; six, the second year; and three, the third year. This procedure can be considered only as a palliative measure for such lesions, but when the grade of malignancy is low, excellent results are obtained.

Diathermy has been used at The Mayo Clinic since 1925 in treating tumors of the bladder that were considered non-resectable on account of their situation in the base and neck of the bladder. When the growths were large and pedunculated, they were partially removed by excision with the cautery, and the remainder were subjected to thorough electrocoagulation. Bumpus, in his study of the early results following this treatment, observed that the length of convalescence was in direct proportion to the extent of the growth, as the slough had to be carried off in the urine, and if the growth was extensive, the process took many weeks. Absorption of protein toxins produced by coagulation of the tissue often caused marked toxemia that was in direct proportion to the extent of the tumor destroyed. The ultimate scar produced after healing was confined to the site of the tumor and was usually broad and not cord-like, as it is after resection or excision. This observation confirms the experimental work of Corbus,[2] who showed that in dogs, capacity of the bladder was not reduced following electrocoagulation of the cystic wall, and the wall remained smooth and elastic, as contrasted with the irritating deformity that sometimes follows resection.

In a recent study of 165 patients who had malignant lesions of the bladder, and who lived five years or longer following various surgical procedures, one of us (Counseller)[3, 4] found that in 17 of the 165 cases, the lesions involved the base of the bladder, ureteral orifices, or both, and were considered non-resectable. Therefore, the lesions were treated by electrocoagulation only in 14 cases; in three the major portion of the tumor was excised with the cautery and the base was subjected to electrocoagulation. Fifteen of the patients were alive at the time of that review, and were free from vesical symptoms.

In view of the favorable results obtained by the use of diathermy in this group, we are reporting on these 17 cases in greater detail, including data from the follow-up records.

Classified with respect to the grade of malignancy of their lesions, four patients had lesions graded four, five had lesions graded three, four had lesions graded two, and four had lesions graded one. The average age of those with lesions graded four was 47 years; the youngest patient was 44

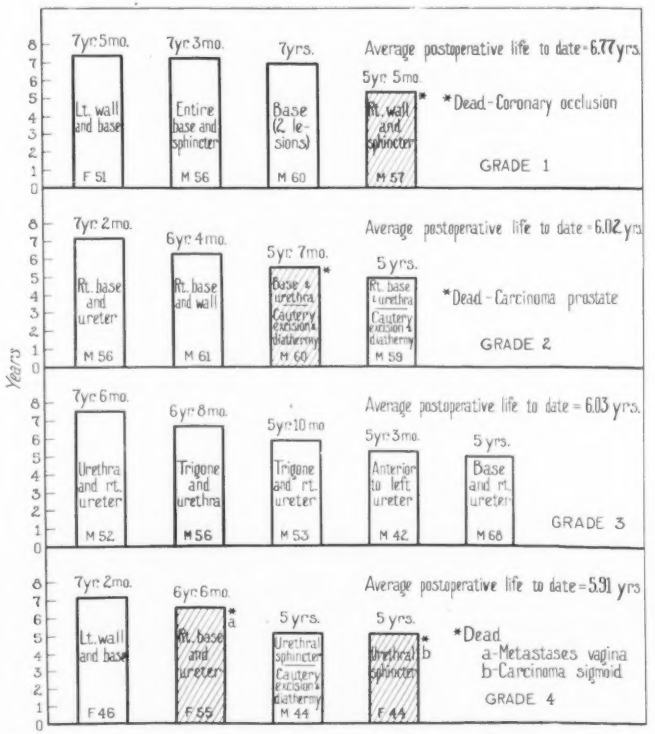
years of age, and the oldest, 55. The average age of patients who had lesions graded three was 54 years; the youngest patient was 42 years of age and the oldest, 61. The average age of patients who had lesions graded one was 56 years; the youngest patient was aged 51 years and the oldest, 60 years. The one significant factor shown by analysis of the ages is that the lowest average age, 47 years, was of those patients whose lesions were the most malignant. Although this group of cases is not large enough to allow definite conclusions to be drawn, one can infer that malignant disease of the bladder conforms to the same general rule that applies to malignant disease elsewhere in the body, namely, the younger the patient with a malignant lesion the greater is the probability that the malignancy is of high grade.

In two cases in which the patients were dead at the time of the previous report the malignancy of the lesions was graded four, but only one patient died of recurrence; the other had an independent malignant lesion of the sigmoid with metastasis to the liver, which was the cause of death, and the bladder was free from recurrence. The patient who died of recurrence had nearly three years of postoperative freedom from the disease before recurrence was noted. Eight months had elapsed between the last follow-up information and discovery of the recurrence. The recurring lesion, which measured two by two cm., was treated by transvesical electrocoagulation. Our efforts failed to get the patient to return for follow-up examination until six months after the recurrence had been noted, instead of at the usual interval of three months. A small, indurated area at the original site of the tumor was fulgurated transurethrally. Three years then passed before the patient returned despite urgent requests for her to return earlier, and then she had extensive recurrence involving the left wall of the bladder, and distant metastasis. She died three months later.

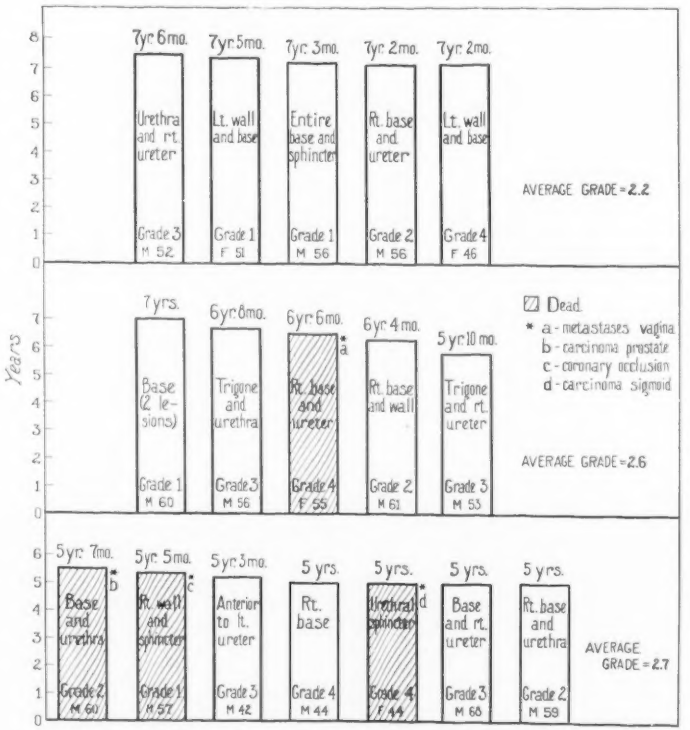
Two other patients have died recently but not from carcinoma of the bladder. One was a man, aged 57 years, who at the time of his original operation had a diffuse lesion, graded one, involving the right wall and urethral sphincter. He lived five years and five months without recurrence and died from coronary occlusion. The other patient who died was a man, aged 60 years, at the time of his original operation (Case X). He lived five years and seven months and died from carcinoma of the prostate gland which involved the base of the bladder secondarily. In the remaining 13 cases the patients are alive and free from any evidence of carcinoma of the bladder. The average postoperative life is the longest for patients with lesions graded one, and the shortest for patients with lesions graded four (Graph 1). The data in Graph 1 are accurate for this group and it is safe to assume that they would be similar in a larger group of cases, although other natural causes of death of patients of higher age groups, such as coronary disease, arteriosclerosis, pneumonia, and so forth, might alter this ratio.

When the cases are analyzed further with respect to duration of postoperative life, it is also seen that those patients living longest had lesions of an average grade of malignancy of 2.2, those living next longest had lesions

Volume 101
Number 6



GRAPH I.—Cases of malignancy of the bladder treated with diathermy by grades, with age, sex, duration of life and location of lesion.



GRAPH II.—Cases of malignancy of the bladder treated with diathermy in order of duration of life, with age, sex, grade and location of lesion.

of an average grade of 2.6, and those with the shortest period of life had lesions of an average grade of 2.7. This is additional evidence that the chance of living out their life expectancy is greatest for patients with lesions in the lower grades of malignancy (Graph 2).

Regardless of the method of removal, postoperative recurrence or extension of the malignant growth may take place (1) in the form of implants; (2) by direct extension beyond the tissue removed; or (3) along the lymphatic vessels. For many years it has been a routine procedure at The Mayo Clinic to request all patients who have been treated for malignant lesions of the bladder to return for postoperative cystoscopic examination every three months during the first year, and subsequently at intervals of six months or a year until five years after operation. If the patient is free from recurrence at the end of this period, he is dismissed from the follow-up records. In this manner many recurrent growths are discovered early and destroyed by transurethral electrocoagulation before symptoms develop, thereby making it possible to improve the end-results materially. It has been repeatedly observed that early recurrences, even of lesions graded three or four, will disappear after simple electrocoagulation. Unfortunately, some patients disregard the follow-up notices and fail to return until there is extensive local recurrence requiring secondary transvesical surgical procedures.

The results of the follow-up records in these 17 cases are recorded in Table I. During the entire follow up period, only two patients had recurrences, one in which the lesion was of Grade one and one of Grade four. This observation may in the future prove to be significant as to the value of diathermy, since the percentage of recurrences following its use is less than with any other form of therapy.

It is said that the extent of the necrosis produced by diathermy amounts to twice the diameter of the coagulating electrode, whereas malignant cells are destroyed to a depth equivalent to three times the diameter of the coagulating electrode. The ureteral orifices could not be found in five instances, as they were covered and partially occluded by the malignant growths. The tumor in these situations was electrocoagulated without regard to the ureteral meatus, and in two instances the intramural portion of the ureter was opened by coagulation one cm. above the ureteral opening. Complete healing occurred in every instance, leaving a clean scar with the ureteral orifice occupying a depression in the scar. Troublesome ascending infection did not occur in any instance. That tumor tissue involving the urethral sphincter may be completely destroyed, as in Case V, without subsequent incontinence or local recurrence, is also of interest.

The absence of local recurrence, particularly in cases in which malignancy is of the higher grades, would tend to indicate that malignant cells are readily destroyed by diathermy well beyond the region of necrosis. Also it is presumptive evidence that extravesical growth of the lesion had not occurred and it should be another argument in favor of early and thorough electrocoagulation of tumors that cannot be resected with safety. The patient in

TABLE I

Results of Follow-up Studies in Carcinoma of the Bladder

Grade of Malignancy	Case	Sex and Age	Known Duration of Postoperative Life		Recurrence, Interval after Operation	Treatment, Type	End-result
			Years	Months			
4	1	55F	6	6	2 years, 6 months	Transurethral diathermy	Died of carcinoma of bladder
	2	46F	7	2	None	None	Dropped from follow-up
	3	44F	5	4	None	None	Died of carcinoma of sigmoid
	4	44M	5	0	None	None	Dropped from follow-up
3	5	56M	6	8	None	None	Dropped from follow-up
	6	53M	5	10	None	None	Dropped from follow-up
	7	42M	5	3	None	None	Dropped from follow-up
	8	52M	7	6	None. Inflammatory questionable carcinoma	Lavage of bladder	Dropped from follow-up Biopsy inflammatory
	9	68M	5	0	None	None	Dropped from follow-up
2	10	60M	5	7	None (?)	None	Died from carcinoma of prostate gland
	11	59M	5	0	None	Lavage of bladder	Dropped from follow-up
	12	56M	7	2	None	None	Dropped from follow-up
	13	61M	6	4	None	None	Dropped from follow-up
1	14	57M	5	5	None	None	Died from coronary occlusion
	15	56M	7	3	None	None	Dropped from follow-up
	16	60M	7	0	4 years	Transurethral fulguration	Dropped from follow-up
	17	51F	7	5	None	None	Dropped from follow-up

Case I, the only one who died of recurrence, perhaps could have been kept free from the disease had she returned for her follow up check when advised to do so.

The inability to distinguish between an inflammatory condition and recurrence by cystoscopic or gross inspection in certain cases is illustrated in Case VIII, Table I. The patient refused to return for reexamination until nearly three years following electrocoagulation. Cystoscopy then disclosed what appeared to be an extensive recurrent growth, and transvesical exploration was advised but was refused. Specimens removed at the time of cystoscopic examination were all inflammatory tissue. However, not infrequently the first specimen removed is reported as inflammatory tissue, and the second specimen may be of malignant tissue. The patient did not return for subsequent examination but in answer to a follow up letter seven years and six months after the original electrocoagulation, he claimed to be in excellent health, although the primary lesion was graded three as to malignancy and involved the urethra and right ureter.

Some postoperative deformity occurred in three instances and in each was associated with rather marked cystitis. In two of these cases in which the deformity was the most troublesome, extensive lesions were partially removed by excision with the cautery (Cases X and XI). The third patient had an extensive lesion confined to the right base and wall and the postoperative deformity, although slight, must be attributed to diathermy. Lavage of the bladder eradicated the cystitis and the patient subsequently reported excellent health. The deformity in the first two instances can properly be attributed to excision by cautery. Indeed, one of the marked advantages of diathermy over resection is the small amount of deformity which results. When a growth is resected or excised, the spherical contour of the bladder is not infrequently destroyed and, as Bumpus stated, there may be a tendency to hour-glass deformity. A bladder so deformed does not usually empty satisfactorily, and the chances of residual infection are great. Although radium was used, either alone or in combination with other procedures, in many of our cases, it was not used in any of these 17 cases. It is of interest, therefore, that not one of the good results obtained in this group can be attributed to radium therapy.

Conclusions

The use of diathermy in the surgical management of carcinoma of the bladder is gradually being extended, for it has brought cases in which the condition formerly would have been regarded as inoperable, or the growth as non-resectable, within the field of successful treatment. Seventeen patients whose condition was considered inoperable were treated extensively with diathermy alone, and 15 of the 17, or 88 per cent, lived more than five years. The two others have recently died from unrelated conditions.

Tumors of the bladder that are comparatively small and are of malignancy of Grades one or two, are usually controlled by transurethral electrocoagula-

tion. Some of the early, circumscribed lesions that are graded three or four and that can be seen easily, and give no clinical evidence of infiltration may be treated similarly. The more extensive, highly malignant lesions and the widespread lesions with low degrees of malignancy are attacked preferably by the suprapubic route. Whenever the lesion can be completely removed surgically, by either segmental resection or excision, this is the operation of choice. For the inoperable lesions of both high and low grades, confined to the base, electrocoagulation is used. The small number of recurrences and the lack of deformity and infection of the bladder would recommend this method of treatment. In some instances these procedures may be combined with the application of radon seeds or of needles containing radium.

It is our impression that the advantages of diathermy as a transvesical procedure for inoperable or non-resectable lesions of both high and low grades have not been sufficiently recognized.

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RADIUM TREATMENT OF CANCER OF THE BLADDER

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Pathology as Affecting Treatment of Bladder Cancer.—The grading of tumors has been of great help in making a comparison of different methods of treatment possible. According to Broders' system, bladder tumors have been graded into four classes. Grade I corresponding to a papilloma and Grades II, III and IV variously increasing degrees of malignancy. The treatment of each grade is discussed separately.

Grade I.—In papilloma radium probably is not indicated; fulguration through the cystoscope or through a cystotomy wound is probably the best treatment. Extensive papilloma of the entire bladder wall is probably best treated by cauterization through the open bladder after the method of Beer.

Grades II and III.—Keyes says, "Experience confirms the impression that tumors microscopically grouped under Grades I and II are almost as curable by radium as papilloma, and should scarcely fall within the popular

conception of cancer." This is a slightly ambiguous statement as papillomata are generally considered a Grade I malignancy. We disagree with the statement in regard to Grade II as we believe that these are real cancer. As far as the grade of malignancy goes Grades II and III can be treated either by surgery or radium.

Grade IV.—Probably the treatment in this class by either radium or surgery is inefficient. We have only one case cured by radium, although Counseller and Walters report a "relative high percentage of five-year cures of patients with tumors graded III and IV." They did not separate the two grades in that article. External radiation, we feel, has been much neglected in the treatment of Grade IV tumors. It should, we believe, precede either surgery or radium implants.

Situation of the Tumor in the Bladder.—(A) Tumors of the base or lateral walls coming in approximation to the ureters or internal urethra are shown by our statistics to be 61 per cent in 78 controlled cases. Tumors of the lateral walls of the bladder base back of the trigone or the vault are 32 per cent with 6 per cent not given. In 165 cases from The Mayo Clinic, these statistics are practically reversed with 66 per cent tumors of the lateral walls and vault, and 33 per cent of the base, trigone, urethra or ureteral orifices. The tumors of the base are handled easily by radon implants either through the cystoscope or the cystotomy wound.

(B) Tumors of the apex are as well handled by radium as by surgery and possibly better by the latter method.

(C) Tumors of a diverticulum are better handled by surgery by the removal of the tumor and the diverticulum. If there is secondary involvement of the bladder, radium may supplement surgery.

(D) Tumors secondary to the prostate are better treated by radon implants through the open bladder.

(E) Tumors protruding from the ureteral orifice and secondary to ureteral tumors are handled by surgery alone. If there is secondary involvement of the bladder, radon implants may supplement surgery.

Size.—With increase in the size of the tumor base radium takes the ascendant over surgery, until there arrives a time when surgery is totally ineffective and radium reasonably effective. This does not mean that all large tumors are cured by radium. Far from it. In 78 controlled cases the base of the tumor in 21 cases (27 per cent) was between one and four cm. In 16 cases (20 per cent) the base was between four and six sq. cm. In 37 cases (47 per cent) the base of the tumor was more than six sq. cm. In 17 cases of these 37 the base was 20 sq. cm. up to and including a half or more of the bladder. In four cases the base was not given. Very large bulky tumors of the top of the bladder even if involving the ureters are better treated by surgery.

Mortality of Suprapubic Implantation of Radon.—In the first series of 109 cases there were four deaths in the hospital, a mortality of 3.6 per cent. In 179 cases there were 13 deaths in the hospital, a mortality of 7.2 per cent.

Dean in 134 cases of radium implantations had nine deaths in the hospital, a mortality of 6.7 per cent.

The reason for our increase in mortality has been that we unquestionably chose cases too far advanced for radon implantation that would better have been left alone. If the patients are properly chosen, if the bladder is handled as gently as possible, no attempted mobilization being made, if alcohol injections are not used, we believe that the mortality should be between five and seven per cent.

Percentage of Cures.—In a certain number of the early cases we did not get an adequate piece of the tumor for pathologic examination, which necessitated throwing out these cases in this series. In 205 personal cases 66 or 32 per cent are controlled; 50 or 24.3 per cent are well three years; 44 or 21.4 per cent are well five years. One of the factors of this low percentage of five-year cures is the fact that many patients come in to us at the Memorial Hospital who have been operated upon before and have tumors that are very extensive when first seen. This is emphasized by the size of the tumor base of the controlled cases.

Analysis of the Controlled Cases.—(A) In 48 cases which are graded there were nine Grade I (not papilloma), 24 Grade II, 14 Grade III, and one Grade IV. (B) The decision as to whether a tumor is operable or non-operable lies in the hands of the individual surgeon who treats the tumor and depends upon the skill and experience of the surgeon. However as far as could be estimated in these 78 controlled cases, 33 were operable and 43 were inoperable, with two borderline cases.

Forms of Radium.—Radon seed implants are peculiarly applicable in controlling bladder tumors. This is not so of element radium in needles. We have nearly always a single plane about one cm. deep to radiate and needles are too clumsy and too large to effectively radiate such a plane. Radium needles also have to be removed while radon seeds do not and there is a great chance that radium needles will be displaced during the process of the treatment.

Disadvantages of Radium Treatment.—Such treatment must as a rule be made in special hospitals where large amounts of seeds are available. One must always have one-third more than the maximum number of seeds thought necessary and the expense of radium has to be seriously considered.

Radium After-Effects. Slough and Stone Formation.—This is a very definite disadvantage and both of these are probably dependent upon infection of the tumor. The more the infection the greater the possibility of a bad slough, and stone formation. The complications after the radium implants in 78 controlled cases were as follows:

Stone in bladder	9
Stricture urethra	1
Infection of bladder and kidneys	2
Infection kidneys	2
Urethrovaginal fistula	0
Urethrorectal fistula	2
Suprapubic fistula	3

The Advantages of Radon.—First and foremost should be placed the ease with which tumors of the bladder base can be implanted. There is a lower mortality than after operative removal. No reimplantation of the ureters is necessary. Large tumors of the bladder base which are quite beyond the scope of operability can often be controlled.

TREATMENT OF BLADDER CANCER WITH EXTERNAL IRRADIATION

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IN EMPLOYING external radiation for bladder tumors the main difficulty consists in delivering into the tumor through a considerable thickness of intervening tissue sufficient radiation to cause complete regression of the tumor without injury to the patient. At present there is no biologic test by which one may learn how much radiation is required to destroy a certain tumor in any given location. However, it is known that epithelial tumors of the skin, similar in structure to bladder cancers, have been successfully treated with external irradiation, and bladder tumors have been controlled with interstitial irradiation from radon seeds. Therefore if the dose of interstitial radiation which has proven adequate to control bladder tumors can be computed and if this can be translated into terms of external irradiation, the quantity of external radiation required to control bladder tumors will be known. Furthermore, if a study is made of the depth doses delivered by the different sources of external irradiation it can be determined whether or not the successful bladder dose can be obtained from these sources.

To determine the amount of radiation required for successfully treating bladder tumors 30 carefully selected case records were studied. Each of these patients was free from disease more than five years after treatment. In each case the size of the tumor had been recorded and histologic examination had proven the growth to be malignant. The treatment in all cases consisted in the implantation of radon seeds, the number and strength of which were known.[1]

It was found that 50 per cent of the patients had received between seven and ten threshold erythema doses, (T.E.D.), 25 per cent had received less than seven T.E.D., and 25 per cent had received more than ten T.E.D. In some cases the tumors were so large that seeds of the usual strength spaced one cm. apart would have furnished a dangerous total irradiation. Therefore weaker seeds were used and the tissue doses were lower. On the other hand, if operations were urgent and the tumors were not too large, strong seeds were used if weaker were not available, and the average tissue dose was exceeded. The amount of irradiation was never altered for tumors of different radiosensitivity. The dose was always maximal and was intended to destroy all tissue in the area treated. Realizing that these figures are

approximate, the average successful dose of radiation for bladder tumors will be considered to be between seven and ten T.E.D. Since the intensity of radiation of radon seeds decreases constantly at the rate of 16 per cent per day, the total dose of radiation is administered practically within the first two weeks.

The sources of external irradiation which may be used in treating bladder tumors are the high voltage roentgen rays with a peak of about 200 kilovolts and the 700-kilovolt General Electric unit which has been employed at the Memorial Hospital in an experimental way for the past two years. The four-Gm. radium pack is not suitable for treating bladder tumors because at 20 cm. distance from the surface of the body treatment would be too prolonged.

By means of physical experiments the percentage of the amount of radiation falling on the skin which arrives at any depth within the body has been determined. Table I shows penetration at various depths for the 200- and

TABLE I

Depth Doses from 200- and 700-Kilovolt Roentgen Ray Units

Depth	200 Kilovolts	700 Kilovolts
	50 cm. T-S dist.	50 cm. T-S dist.
cm.	0.5 Mm. Cu. and	5 Mm. Cu. filter
	2.5 Mm. Al. filter	100 sq. cm. portal
	100 sq. cm. portal	
0	100	100
2	94	94
4	75	79
6	59	67
8	44	53
10	33	42
12	25	33
15	17	25

700-kilovolt units with the conditions under which they are most commonly used. From this table if the amount of radiation falling on the skin at each portal is known, and if the depth of the tumor below each portal has been determined, the tissue dose from external irradiation can easily be computed. Fig. 1 represents a cross-section of a pelvis of an average sized individual showing irradiation of the bladder by high voltage roentgen rays through four skin portals. When each portal receives a full skin erythema dose (100 per cent S.E.D.), at a single exposure the total tissue dose throughout the bladder region is about 120 per cent of a threshold erythema or 1.20 erythema doses.

Measurements of 50 female pelves showed the average anteroposterior diameter to be 20 cm. and the average lateral diameter 34 cm. The average of about 20 male pelves was somewhat less. For simplicity of computation the measurements of the female pelvis will be used. The average depth of a bladder tumor will be arbitrarily placed ten cm. from the anterior and posterior body surfaces and 15 cm. from each lateral surface.

Obviously this quantity of radiation is inadequate for treating bladder tumors. However, the dose delivered by the 200-kilovolt tube may be substantially increased by changing certain factors. By increasing the target skin distance from 50 to 70 cm., using two mm. of copper as a filter instead of 0.5 Mm., enlarging the size of the portals from 10 by 10 cm. to 10 by 15 cm., and employing a fractional dose technic, about four threshold erythema doses can be delivered to a bladder tumor in 16 days.

The fractional dose method of treating deeply situated tumors conserves the skin at the portals by administering suberythema doses of radiation at each treatment and allowing partial regeneration of the skin before subsequent treatments are given. Physical tests and clinical observations have shown that the skin regeneration is considerable. Regeneration of the tumor between treatments is reduced to the minimum because it receives irradiation

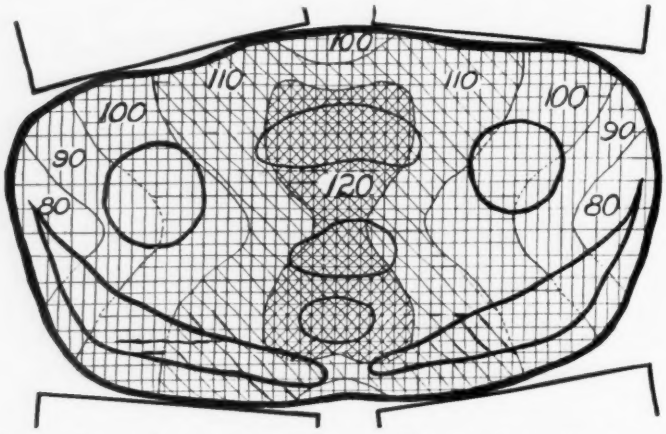

FIG. 1.—Cross-section of pelvis showing irradiation of the bladder by 200-kilovolt roentgen ray unit through four skin portals.

daily. The shorter the time required for administering a cycle of external irradiation the less the tumor regenerates. Treatment of a bladder tumor by interstitial irradiation requires about 16 days because that is approximately the period of activity of the gold radon implants. Therefore in attempting to adopt external irradiation for the treatment of bladder tumors not only must the total dose amount to between seven and ten S.E.D., but the time required for the cycle should not exceed 16 days. Under these conditions the use of the 200-kilovolt tube fails to meet requirements by about 50 per cent.

Clinical experience and physical measurements show that the 700-kilovolt unit offers promise. Using a target skin distance of 60 cm. and filtration equivalent to five mm. of copper, six pelvic and one perineal portal are outlined on the patient. The anterior and posterior portals are 15 by 15 cm., the four lateral and the perineal portals are each 10 by 15 cm. The patient is treated daily with 400 roentgens (r), delivered to each of the portals on opposite sides of the body until each of the pelvic portals has received 2,400r, and the more sensitive perineal portal has received 1,200r. Under these

conditions the bladder tumor receives eight S.E.D. in 20 days. Experience has shown that all patients cannot tolerate such intensive treatment. When this is the case, each exposure is reduced to 300r, an amount which is well tolerated, but the period of treatment must be prolonged to 26 days to furnish a total of eight S.E.D. to the region of the bladder tumor. In spite of the time difference, this method of irradiation so nearly approximates that furnished by gold seeds in the group of successfully treated patients that the method should be used when facilities permit and the judgment of the urologist determines that it is indicated.

The following case report shows that external irradiation can produce remarkable regression in a far advanced inoperable bladder cancer. It will be noted that the amount of radiation in each fractional dose and the time required to complete the cycle vary considerably from the procedure recommended above. These differences are due to the fact that at the time this patient was treated the use of the 700-kilovolt unit was in the experimental stage and it was somewhat later that the methods which are now employed were adopted.

CASE REPORT.—Patient A. B., a 70-year-old Italian laborer, unable to work on account of his present illness, was first seen at the Memorial Hospital November 29, 1932. In April, 1932, seven months before admission, the patient noticed blood in his urine. It was present for three days. He consulted his physician, who referred him to an urologist, but, as the bleeding stopped, the man delayed until bleeding recurred six months later. After a thorough examination the diagnosis of a bladder tumor was made and the patient was referred to the Memorial Hospital. There had been some loss of weight and for two weeks previous to admission there had been chills and fever.

Physical examination showed an elderly man in poor general condition. Rectal palpation showed a large mass above the prostate on the left side, evidently a bladder tumor which had nearly, if not quite, infiltrated through the bladder wall. Cystoscopic examination was difficult because of hemorrhage, nevertheless a large excavating tumor was seen on the left side of the bladder base posteriorly. Specimens were removed for histologic examination and the report of the pathologist was "Infiltrating Epidermoid Carcinoma, Grade III, radioresistant." Roentgenologic examination revealed no metastases in the pelvis or lumbar spine. Urea nitrogen was 23.2 mg. per 100 cc. of blood, hemoglobin 80 per cent, red blood cells 3,900,000, and the differential count normal.

Because of the poor general condition of the patient and the extensiveness of the tumor it was decided to treat him with external radiation using the 700-kilovolt unit. Six portals were used and 500r were given daily until each portal had received a total of 2,000r. In this way about five S.E.D. was delivered to the bladder tumor in 44 days. The patient suffered no discomfort from his treatment. A month after treatment started he seemed somewhat stronger. Two and one-half months after treatment was started and a month after the first cycle had been completed the bladder tumor was smaller and rectal palpation revealed a marked diminution in the amount of induration at the bladder base. As the skin was in good condition and because we had never seen lasting benefit from treatments of four S.E.D. in other cases, another cycle was given at this time identical with the first.

This patient received ten S.E.D. delivered to the bladder tumor in three and one-half months. The skin was blistered after the second cycle, but the man was able to return to his usual occupation and he steadily gained weight. When the second cycle was finished cystoscopic examination showed generalized congestion of the bladder but no tumor could be found. At present, 30 months after admission, the patient looks and feels well.

He is working regularly. He has gained 30 pounds. Urinalysis is normal, the interior of the bladder looks normal, and no induration can be felt per rectum.

Conclusions

(1) The average successful dose of radiation for treating bladder tumors is about seven to ten S.E.D. delivered within 16 days.

(2) The four-Gm. radium pack is not suitable for treating bladder tumors on account of the time required to administer a satisfactory dose.

(3) The 200-kilovolt unit can furnish about 50 per cent of the required dose. Therefore it offers slight hope of curing a bladder tumor. Even its palliative value is questionable.

(4) The 700-kilovolt unit can so closely approximate the required dosage that one is justified in employing it to cure bladder cancer. It is assumed that a complete urologic examination has been made in all cases and that the choice of therapy has been made by the urologist.

The writer wishes to express his appreciation to Mrs. Edith Quimby of the Department of Biophysics of the Memorial Hospital for her assistance in the preparation of this paper.

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THE UPPER URINARY TRACT IN CARCINOMA OF THE BLADDER

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Tumors of the bladder are habitually epithelial in origin, projectile in character, invasive in nature, indolent in progress and possess a disposition to be situated upon the mucous membrane of the bladder very frequently in the region of the trigone and base, in most instances not far remote from the ureteral orifices. They manifest their presence by a well-defined signal, hematuria, which is so characteristic that it should always excite suspicion and call for immediate investigation but unfortunately the signal is not heeded and in our series of well over 500 cases of tumor of the bladder the average duration of this striking symptom, before special investigation was sought, was two years and eight months, a sufficient time to allow many of the tumors with their particular susceptibilities to create other destructive effects. Because of their striking predilection to localize themselves near the ureteral orifices and their decided tendency to infiltrate the wall of the bladder it is not extraordinary that we should expect them to exercise a material detriment to the outflow of urine from the kidney.

The problem of the fate of the upper urinary tract in carcinoma of the bladder is of exceeding interest and of supreme importance. Some of the information which has been secured from examining the cases in my service

may stimulate others to appreciate, respect and investigate this important phase of bladder neoplasm. I have been able to analyze only 300 of the cases of bladder tumor with respect to their relationship to renal disease.

Medical literature furnishes but little practical knowledge respecting the fate of the upper urinary tract when carcinomatous lesions invade the urinary bladder. It is striking that this phase of the subject has received but scant attention despite the fact that ureteral obstruction is not an infrequent accompaniment of carcinomatous lesions which invade the trigone of the bladder. Every tumor of the bladder, regardless of the result of cystocopic or biopsy study is from the clinical standpoint potentially malignant and the remarks which follow apply in a measure to all tumors of the bladder. The continued well-being of a patient with carcinoma of the bladder is materially influenced by the preservation of his renal function and when this fails to withstand the vicissitudes imposed by the disease he becomes encumbered by an overwhelming infection to which he quickly succumbs. The logical conclusion to be drawn from a study of the life history of vesical tumors is that an individual who harbors a tumor in his bladder which remains untreated and if he does not die from the ravaging effects of the growth or hemorrhage will eventually do so from urosepsis. The immediate cause of death in the majority of cases is not due to involvement of vital organs such as the liver, bone, lung, *etc.*, which are the sites of predilection in cancer of the prostate, nor carcinomatous extension of the growth or its metastatic products into contiguous organs such as the rectum. If they survive the debilitating influence occasioned by depletion of their blood stream as a result of repeated or continuous bleeding they frequently die a renal death. The upper urinary tract may be called upon to bear the brunt of the attack when an invasive tumor in the bladder is so situated that it interferes with drainage, resulting in hydronephrosis and hydro-ureters which may subsequently become infected, pyonephrosis and the conversion of the kidney into a functionless sac. Such renal involvements may eventuate from a superficial invasion of the vesical mucosa thereby interfering with the ureterovesical valve with the production of regurgitation which occurred in 24 per cent of the cases upon whom cystograms were made. These were the cases in which an involvement of the ureter was suspected and constituted only 3 per cent of the total cases, in other words only 12 per cent of the cases had cystograms made. They may result from vesical wall invasion with occlusion of the intravesical ureter or from extravesical ureteral obstruction resulting from outside extension or glandular invasion. Cystographic study showed that 50 per cent of the cases examined had ureteral regurgitation without any evidence of vesical wall infiltration as characterized by filling defects. Such cases usually represent a superficial mucosal growth and are more susceptible to cure. The other 50 per cent with regurgitation showed definite vesical wall indentures due to invasion and in such instances a more serious prognosis is predicted not only relative to the tumor but also to the future of the kidney. The patient may die an uremic death whenever the obstruc-

tion occurs rapidly. The failure to recognize this eventuality imperils the patient's life and may bring it to a very abrupt termination whereas its presence when detected and alleviated or corrected by appropriate and timely measures such as catheter drainage, ureterostomy or nephrostomy permits of consummation of the therapeutic régime instituted for the carcinomatous lesion in the bladder and in certain selected cases of lesser malignancy eventual cure.

The bladder cannot be regarded merely as a storehouse for the secreted urine until it is ready to be expelled from the body nor as a separate reservoir. It comprises a segment of an elaborately designed conduit system of which it forms a part which is provided with accurately coapted valves or sphincters which regulate the flow of fluid in its interior. Interference with drainage will result in disruption at the flood gates and the upper urinary tract will be converted into a stagnate pool which becomes an ideal nidus for bacterial implantation and growth and eventually renal destruction as a result of urosepsis. Fortunately blockage of the urinary tract is infrequently encountered with benign tumors because there is very little or no infiltration of the bladder wall but it is not an infrequent accompaniment of carcinomatous tumors and in particular those of the infiltrating type.

The provision of adequate urinary drainage is the *sine qua non* which governs the maintenance and preservation of normal renal function. Any impediment will obviously disturb this equilibrium and create a hazard which later may become difficult to surmount. Tumors of the bladder which are of the papillary type with very little or no tendency to infiltrate the deeper layers of the bladder, situated in areas distantly removed from the ureteral sites, such as the dome of the bladder, unless they are of such proportions that they block the orifices or the internal neck at the sphincter will obviously exert no profound effect on drainage of the upper urinary tract. It is with the nodular or infiltrating type of growth which histologically manifests a marked degree of atypism in the cancer cell (Grades III or IV malignancy) which has a broad base and ragged edges and in which ulceration of the surface proceeds *pari passu* with tumor formation and which displays decided propensities for local invasion, that renal function is endangered. Moreover, malignant invasive tumors occurring in the immediate vicinity of the ureteral orifice not infrequently affect the integrity of the ureterovesical valve. Incidentally the presence or absence of demonstrable reflux or regurgitation of fluid into the corresponding ureter and kidney may be relied upon to furnish valuable prognostic data regarding the invasive tendencies of the tumor concerned and its adaptability for radical resection or irradiation.

Clinically, the incidence of one-sided renal pain is of grave significance since it points to pressure on one ureter and the risk of pyelonephritis. An aching pain in the renal region caused by dragging of the tumor growth on the corresponding ureter is not infrequently complained of and in our series of cases was occasionally encountered. This symptom may mislead the surgeon into suspecting a renal origin for the hematuria. I have records of

two cases whose kidneys were removed by other surgeons. Some bladder tumors will kill in a few months, others will grow slowly and may be present for from 10 to 20 years. It is sometimes astonishing to find how long the patient may linger even though his agony is intense and his bleeding continual. Unfortunately many bladder tumors first come under observation too far advanced to cure them and an attempt is made to palliate the patient's condition rather than cure, although we know full well that the disease will invariably be fatal if left alone.

After a cystoscopic examination has been made and the nature of the tumor estimated, the location of the growth in the bladder should be determined and in particular its relation to the ureteral orifices and the internal sphincter. In this series 78 per cent of the cases of tumor were located on the base and low lateral walls, 8 per cent were general, 7 per cent immediately around the ureteral orifices and 7 per cent at the dome. Two of the dome tumors caused such extensive invasion of the bladder wall as to occlude the ureter. Evidences of infiltration of the trigone and the rectovesical space detected by rectal or vaginal examination may be of inestimable value in determining the infiltrative characteristics of the growth.

Granted that there is a malignant tumor in the bladder possessing varying degrees of invasive tendency and malignancy which will require treatment by surgery, irradiation, fulguration or a combination of these physical agents, what steps must be taken to safeguard preservation of renal integrity? The patient may die of uremia or urosepsis even before there is involvement of the regional lymph nodes. In a series recently studied by G. G. Smith, distant metastases were found in about 40 per cent of the cases, in Beer's series the presence of these growths was considerably less and in our series it was not over 25 per cent.

What are the aids at our disposal to determine the extent of the damage which has been imposed on the kidney and ureter? Repeated blood urea nitrogen estimations, the determination of fluid intake and output and the concentrating power of the kidney by the Mosenthal or urea concentration tests provide relative information regarding the adequacy of renal function. The index of elimination representing the combined renal functional capacity, employing such dyes as indigo-carmine or preferably P.S.P. offer corroborative evidence regarding the efficiency of renal function. This data when supplemented by clinical evidence of tissue dehydration and otherwise impaired physical status of the patient provide concrete facts relative to the advent of renal failure.

In the series of 300 cases recently studied there was evidence of renal infection in 21 per cent, this closely parallels Barringer's findings of 16 per cent. In order to estimate the effect of the growth upon kidney efficiency we surveyed the patients upon whom studies of blood nitrogen retention or excretory tests particularly phthalein were made. One hundred and forty-four cases of this series were so studied or 48 per cent of the total. The remainder were more or less ambulatory patients in whom no suspicion of

kidney disease was entertained. It is quite possible a number of them possessed varying degrees of renal disturbance. In this series of 144 cases, 64 or 44 per cent showed diminution of renal function.

In the series of 300 cases there are records of death in 90 and of these 25 came to postmortem. There was definite evidence of renal disease in 34 or 38 per cent. Of the 25 cases which came to autopsy, 15 or 60 per cent died a renal death.

The value of intravenous urographic studies cannot be too strongly stressed as the best method for determining the status of the involved kidney when the ureteral orifice on the corresponding side cannot be visualized or is embedded in the tumor growth or for technical reasons will not readily permit of retrograde catheterization. The radiographic evidence of pronounced pyelectasis calls for drainage by ureter catheter or in the event this is not possible or feasible by ureterostomy or nephrostomy. Intravenous urography is also an useful aid and in fact the only reliable method for determining the fate of the upper urinary tract following ureteral transplantation into the bowel.

The choice of treatment for malignant tumors of the bladder is determined principally by their site, extent, grade of malignancy, and the experience of the surgeon. Personally the treatment of bladder cancer by the closed or endoscopic method is elected because I have found but few bladder tumors which could not be effectively controlled by fulguration, supplemented by radon seed implantation. In dealing with tumors in the immediate vicinity of the ureteral orifices the operator must be cautious lest the reaction following fulguration or implantation result in temporary occlusion of the ureter with a resultant acute pyelonephritis. Another danger which must be constantly kept in mind is that fulguration in this vicinity may lead to stenosis of the ureteric orifice and insidious but progressive destruction of the kidney. The amount of heat generated in the growth should be estimated by its destructive effect rather than by the gyrations of the ammeter needle. Intensive coagulation near an orifice at one sitting is to be condemned unless a snare electrode can be employed to remove the projecting portion of the growth and effectively fulgurate its pedicle and base after determining its proximity to the ureteral orifice. I am not inclined to agree with Bumpus that massive destruction at one sitting requiring one-half hour or more is the ideal *modus operandi.* Concentration of heat on the pedicle may result in late sloughing or erosion beyond the confines of the tumor and may in addition have a permanently destructive effect on the ureter in the immediate vicinity even leading to late stricture formation and irreparable renal damage. Presumably the total disappearance of a benign tumor after a single application of this current can be accounted for by concentration of heat on the pedicle. It may be advisable to elevate the tumor and visualize the ureteral orifice prior to coagulation in a manner of the ring clamp used after suprapubic exposure of the tumor for surgical diathermy. The ureter catheter may be useful for temporary drainage when extensive fulguration or im-

plantation is required and whenever there is imminent danger of ureteral obstruction due to the development of marked edema in the vicinity of the ureteral orifice. I have for years relied upon the combination of electrocoagulation and radon seed implantation through the cystoscope in the great majority of bladder tumors, in most instances repeatedly applied, because the results have been so astoundingly superior to any type of surgical procedure which had been previously employed. I have never seen an extension of the reaction accompany the application of radon seeds beyond the confines of their application after the immediate reaction was over. An extension of a reactionary process has always been the result of the tumor growth and I do not believe that we may look for late extension from seed implantation. I have seen innumerable instances of typical radium ulcers remain localized for months and finally disappear without lateral extension. A number of these tumors of the bladder have been the result of extension of carcinoma of the cervix of the uterus. Doctor Newell of the Department of Gynecology of the Washington University has analyzed 400 cases of carcinoma of the cervix, 12 or 3 per cent of which invaded the bladder. Fifty per cent of these patients died of kidney involvements. Thus whether the tumor is primary in the bladder or secondary from extension, it tends to invade its wall and produce ureteral occlusion. There were several interesting cases in this group following radium implantation in the cervix which I examined several months to five years after the application of radium, because of vesical distress. In these instances there was always a localized pale scarred area on the base of the bladder in the region of the cervix with extensive arborization of vessels and in some instances superficial ulceration. These were proved to be radium reactions and in no instance was there extension with involvement of the ureter.

The surgical treatment of cancer of the bladder by resection, excision, cauterization with or without the application of surgical diathermy or radium implantation suprapubically or total cystectomy may entail reimplantation of the ureter into the bladder, bowel or cutaneous surface. Watson was among the first to recognize the importance of preliminary diversion of the urinary stream in order to preserve renal integrity and he advocated bilateral nephrostomy before cystectomy was performed. Some surgeons still prefer this procedure to transplantation of the ureter into the bowel. Whether it is advisable in performing resection of the bladder tumor to preserve the ureteral orifice or remove the tumor and bladder wall *en masse* is problematical. Beer states that he has no hesitation in doing the latter and states that his end-results are more satisfactory than when attempts have been made to spare the ureteral orifices. I have performed a fair number of resections with ureteral transplantation into other portions of the bladder wall and frankly admit my almost universal disappointment in the end-result, which has usually been an atrophic kidney.

Ureteral transplantation into the bowel when performed should be so devised that it aims at reconstruction of a valve at the lower extremity of

the ureter at its point of entrance into the bowel. The transference of a hollow channel into another of similar structure but larger dimensions is apt to result in stenosis regardless of the perfection of the operative procedure employed. I am fully aware of the excellent results which have followed its performance in the hands of experienced surgeons but the majority which I have observed have been far from satisfactory. The Higgins' operation of "aseptic uretero-intestinal anastomosis," employing the transfixion suture aiming thereby to promote fistulous formation between the ureter and the contiguous bowel and extraperitoneal cystectomy later with ligation of the ureters where they emerge from the trough in the bowel wall, appeals to me as being the most feasible from a physiologic standpoint and one which may preserve renal integrity. The fistula begins to function within 24 to 48 hours after operation and intravenous study will determine when the cystectomy can be performed safely. I do not share the opinion of those surgeons who advocate this procedure for carcinoma of the bladder and I feel that its performance should be reserved for cases of exstrophy only. Ureterostomy into the skin of the flank or groin is much more preferable for diversion of the urinary stream. Barringer also looks with disfavor on the practice of total cystectomy and ureteral transplantation and advocates radium implantation, whereas Beer believes that a one-stage total cystectomy with ureterostomy into the inguinal regions in infiltrating growths which involve the neck of the bladder as well as the adjacent trigone and lateral walls or when partial resection seems impossible is the ideal procedure.

Coffey was among the first to advocate ureteral transplantation for inoperable carcinoma of the bladder. He advocated his technic of submucous implantation (No. 2) for all cases in which it was necessary or advisable to dispense with the bladder "having due consideration for the physical condition of the patient and the availability of adequate surgical skill." In the male he advocated cystectomy in addition to transplantation and in the female radium implantation into the bladder as well as radium bombing from the vagina. Whenever it was necessary to remove the bladder he advised that this be carried out at a second operation. In a considerable number of his cases he found some dilatation of the ureters as well as an intermittent pyelitis for a few months following operation. Unfortunately he was not privileged to study a large enough series to determine the end-results on renal function. In some cases he observed no alteration in the kidney as revealed by intravenous urography or chemical studies of the blood but the intravenous dyes were not available for his earlier cases and the criterion of renal adequacy in the majority was the apparent well-being of the patient. He reported only nine cases in which he had performed total cystectomy and bilateral ureteral transplantation into the bowel in one stage for carcinoma of the bladder.

The effects of irradiation on the cancer cells are beyond the scope of this paper but their influence on ureteral integrity and the development of occlusion is comparable to the reactions induced by excessive electrocoagulation

at the same site. The incidence of extensive edema of the bladder mucosa at the site of irradiation or implantation and occasional sloughing is due to the caustic effects of the alpha and beta rays. This in itself indicates a preference for the use of gold radon seeds or the gaseous emanation in which these rays have been filtered and it is with a great deal of pleasure that I note that the radium emanations or radon rather than the element are used to the exclusion of all other forms of irradiation at the Memorial Hospital. Doctor Barringer was among the first to popularize the use of radium treatment for malignancy of the bladder in preference to radical resection or total cystectomy and this agent remains today the most formidable weapon we have in the fight against cancer. Radium implantation either cystoscopically or suprapubically when applied promiscuously may result in severe reactionary edema around the ureteral orifices with temporary occlusion or late stricture formation and possibly irreparable renal damage. It may be advisable to elevate the tumor and visualize the ureteral orifices before implanting the seeds and if need be insert a ureter catheter to facilitate renal drainage during the period of irradiation. Infiltrating growths in this vicinity are more prone to jeopardize renal function and the use of radium must not be undertaken too lightly. I prefer wherever it is feasible to amputate the tumor by the high frequency loop and then under accurate visualization implant radon seeds at proper intervals in its base. Tumors near the ureteral orifice if treated in this manner allow the operator to avoid the orifice or at least to understand its exact location and safeguard it. The use of deep roentgen ray therapy in the treatment of cancer of the bladder has proven disappointing on account of its failure of penetration to the tumor site and the inadequacy of gamma radiations but the dangers of ureteral occlusion are nevertheless preëminent.

SUMMARY

(1) It is therefore apparent that disturbances of physiologic activities of the kidneys and ureters occur in a large proportion of malignant tumors of the bladder and contribute at least 50 per cent of the mortality rate.

(2) Early diagnosis of bladder tumors affords the most substantial protection against such involvements. Likewise prompt therapeutic care before invasion has become pronounced is vital to renal security.

(3) The decided tendency of the majority of tumors of the bladder to be located in the neighborhood of the trigone, their pronounced inclination to invade and their likelihood to secondary infection makes the fate of the upper urinary tract precarious.

(4) Safeguarding the ureter is an essential feature in the technical therapy of bladder tumors and every precaution should be exercised to protect it from trauma and insult. It has been my personal experience that the safest and most satisfactory procedure in the treatment of bladder tumors is the application of radon seeds and coagulation, either suprapubically or preferably endovesically. Erosive destructive tumors which implicate the ureter

occasionally require resection with reimplantation. Many of these, however, may be satisfactorily treated by intravesical implantation guarding the ureteral orifices by an indwelling catheter. Reimplantation of the ureter in the hands of the average surgeon is fatal to the kidney. In cases with general carcinomatous change throughout the bladder cavity actual cauterization with or without radon seed implantation occasionally yields gratifying results. The ureteral orifices must always be respected. Total cystectomy has a limited field but when performed demands preliminary ureteral drainage preferably through an iliac cutaneous implant, rarely preliminary uretero-intestinal anastomosis. Ureterostomy or nephrostomy are occasionally necessary as palliative measures to relieve suffering and prolong life.

BRIEF COMMUNICATIONS AND CASE REPORTS

PYELO-URETEROPLASTY FOR STRICTURE *

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CASE REPORT.—Mrs. C. W., aged 50, had had a thyroidectomy performed in 1930. In August, 1932, she experienced a severe, knifelike pain in the right lower quadrant of the abdomen. The pain did not radiate but was accompanied by marked hematuria. A second attack occurred one month later, this time accompanied by hematemesis. During the year she had six recurrences, all of great severity but none accompanied by hematuria or hematemesis. The pains radiated to the genitalia and the thigh. At the time of her last attack in July, 1933, a pyelogram was made showing a kinked ureter.

She entered Lenox Hill Hospital in September, 1933. The general physical examination was negative. The urine showed some albumen and red blood cells. A pyelogram at this time showed a dilated right pelvis with a kink in the ureter and a constriction just below the pelvis. The ureter in its middle portion appears dilated but there was no constriction or obstruction demonstrable to account for this. Kidney function tests showed both kidneys to be functioning normally.

Operation.—On September 27, 1933, the kidney and pelvis were exposed through a Bergmann-Israel incision. A longitudinal incision in the axis of the ureter and extending into the pelvis was made. No aberrant vessel or fibrous band was observed as being the cause of the kink. The incised ureter and pelvis were closed transversely. Cigarette drain to ureter. Recovery was uneventful.

Ormond[1] has considered plastic surgery of the ureter, illustrated by many diagrams. The simplest form of plastic is the Heinecke-Mickulicz type, which was done in this case. It is often designated as Fenger's operation. Schwyzer proposed a Y-shaped incision to bring the V-shaped flap between the upper arms of the Y into the vertical portion of the incision. A third method used by some surgeons is to divide the ureter and reimplant it into the dependent portion of the pelvis.

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HORSESHOE KIDNEY WITH STONE

DR. PAUL K. SAUER presented G. M., a male, aged 47, who in June, 1934, stated that six weeks previously he had noticed that his urine was dark and red following a severe attack of pain in the left lumbar region which had radiated to the genitalia and left thigh, stating that in previous years he had noticed polyuria following such attacks. The general physical examination was negative, except for tenderness in the left lumbar region. Urine

* Presented before The New York Surgical Society, December 12, 1934.

normal except for red blood cells. Intravenous urography demonstrated a definite horseshoe kidney with good and equal function on both sides. The ureters were normal. A stone was visible in the lower calix on the left side. A catheterized specimen from the left ureter showed good function and many red blood cells.

Operation.—June 9, 1934, the kidney and ureter were exposed through a Bergmann-Israel incision. The continuation of the lower pole and its fusion with the right kidney were palpated across the midline. The ureter was exposed crossing over and in front of the kidney. The pelvis was incised and a small stone, the size of a pea, was found imbedded in the lower calix, and removed. The incision in the pelvis was closed with fine chromic gut, a cigarette drain placed to this point. Recovery was uneventful.

This case is presented because it offers several points of interest. It is the most frequent anomaly in form. At the Mayo Clinic out of 2,424 kidney operations performed, horseshoe kidneys were found 17 times; a proportion of 1:142. Lowlsey found the proportion to be 1:600, and Carlier and Gerard found 80 horseshoe kidneys in 68,000 autopsies; a proportion of 1:850.

It is astonishing, in reviewing the literature, to find that so few cases are diagnosed before operation. Judd[1] reported 17 cases, of which nine were diagnosed before operation. Eisendrath[2] collected 132 cases and found that in only nine instances was the diagnosis made before operation. Of course, many of these cases were reported before the advent of roentgen rays. Stone in the kidney is the most common complication of this anomaly.

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DOUBLE ECHINOCOCCUS CYST OF LIVER *

TREATED BY MARSUPIALIZATION

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CASE REPORT.—A male, 18 years of age. Admitted to the hospital March 10, 1934. A native of Maryland, of Italian parentage, who at the age of eight was taken to live with relatives in Italy, where he remained until two years ago. *Chief Complaint.*—A large mass in the left upper quadrant of the abdomen.

Present Illness.—About one year before admission, the patient first noticed a fulness in the left epigastrium and left hypochondriac region. This gradually increased in size, it being particularly noticeable after meals. There was no pain until a few months ago, when a heavy feeling with pain in the region of the liver began to be felt. This had become very much accentuated during the past three days. Two and a half weeks before that the patient vomited. There was no hematemesis, but following the vomiting there was a bloody stool. There had been no loss of weight.

Physical Examination.—Patient not acutely ill, well nourished and developed, presenting a soft mass about ten centimeters in diameter in the left epigastrium and left hypochondrium near the left costochondral junction. The mass crepitates on pressure and deep inspiration. There is a leathery friction rub on auscultation. A diagnosis of echinococcus cyst of the liver was made on admission.

* Presented before the New York Surgical Society. December 12, 1934.

Blood Count		Blood Smear		Feces	Urine
Leukocytes	7,400	Polynuclears	53%	Negative for blood, parasites and ova	Specific gravity 1,014
Polys	80%	Basophiles	5%		Acid
Erythrocytes	4,900,000	Large lymphocytes	3%		No albumin
Hemoglobin	76%	Small lymphocytes	26%		No sugar
		Eosinophiles	12%		Micro.:—Neg.
		Transitionals	1%		
		No abnormality among the erythrocytes.			

A flat radiogram of the abdomen failed to reveal any positive finding. A gastro-intestinal series revealed an extragastric mass in the right hypochondriac region. The chest was negative. The patient had a normal temperature (99°). His blood pressure was 110/80.

First Operation.—March 19, 1931. Under spinal anesthesia, using .12 Gm. of neocaine, the abdomen was opened through a left rectus incision extending from the costal margin to the umbilicus. There was a large yellowish cyst occupying the lower border of the liver. The liver was examined for additional cysts and one about the size of a grapefruit was found on the under surface of the right lobe. The wall of the cyst was sutured to the parietal peritoneum and the abdomen was closed in layers. On the right side a modified Kocher incision was made along the costal margin beginning at the outer part of the rectus muscle, dividing internal and external oblique and transversalis. A large mass was found on the under surface of the liver. It was impossible to approximate the wall of the cyst and the parietal peritoneum on this side, so that portion of the abdominal cavity just external to the gallbladder was packed with gauze in order to develop adhesions which would wall off this portion from the general abdominal cavity and provide an approach to the cyst. His immediate condition was good.

Second Operation.—March 26, 1931, under spinal anesthesia, the clips were removed from the incision in the left rectus. The cyst, which was now adherent to the peritoneum, was opened and the fluid contents suctioned off. Within this cyst was found a smaller cyst, yellow in color and probably the inner layer of the original cyst; it was removed. The cyst cavity was then irrigated with a 1 per cent formalin solution. This was aspirated, and the cyst cavity packed with plain gauze.

The wound on the right side was then opened and the gauze packing removed from the cavity. At this time, the adhesions were not thought to be sufficiently developed to protect the peritoneal cavity from the contents of the cyst. So this cavity was again packed with gauze and the wound closed in order to await the development of stronger adhesions. The patient's condition remained excellent, except that after a few days he developed a rash over a great part of his body and on that account the third operation was postponed until April 7, 1931, when again a spinal anesthesia of neocaine was used.

Third Operation—April 7, 1931. The wound on the right side of the abdomen was reopened. The packing used to wall off the peritoneal cavity was removed. Adhesions had formed, closing off this space from the general peritoneal cavity. The under surface of the liver could now be reached through this approach and the cyst wall was punctured and a clear fluid aspirated; about two quarts were removed. The opening was enlarged and the large cyst removed in one piece. This was smaller than the cyst which had been previously removed from the left side. The cavity was then repacked with plain gauze.

Pathologic Report of Cyst Lining.—April 7, 1931. Gross specimen consists of a large cyst about five and one-half inches in diameter containing a

clear watery substance. The wall of the cyst is white in color, elastic, and consists of two layers—an inner, soft, gelatinous layer and an outer, tough, elastic layer. Both surfaces are perfectly smooth. Microscopic section shows thin layer of fibrous tissue forming cyst wall. Smear taken from the wall of the cyst reveals numerous typical echinococcus scolices, which appear as small circular bodies possessing a rostellum of hooklets. Diagnosis. Tenia echinococcus from a hepatic cyst.

On April 24, 1931, the packing was all removed from the left side and the cavity practically closed. The cavity on the right side, however, was repacked with iodoform gauze and drained for a very much longer time than the left side. The patient had no complications during his convalescence, and was discharged from the hospital on May 28. He has remained well since that time.

Dr. Robert H. Kennedy remarked that the preoperative diagnosis of echinococcus cyst was rather exceptional in this country. Several years ago he had a patient who illustrated this point. A Syrian woman, age 52, had been in this country for 14 years. She had had recurring attacks of pain for four years, thought to be gallstone attacks. She was brought into Beekman Street Hospital in May, 1926, with a temperature of 101°, a rigid right upper quadrant, and a liver enlarged to about four fingers breadth below the costal margin. Her blood count showed white cells 14,500, polymorphonuclears 90 per cent. There was a moderate jaundice, some bile in the stools and considerable bile in the urine. She was quite emaciated. The daily temperature reached 101°. The gallbladder did not visualize after the dye test.

On her fifth day in the hospital she had a chill with temperature 105° and a continuation of the signs in her right upper quadrant. We felt that she probably had a ball valve stone in the common duct with infection of the biliary tract. Operation on the day following the chill demonstrated the gallbladder somewhat enlarged, thin walled, emptying perfectly well, and found nothing in the common duct or pancreas. The liver was generally enlarged and over a number of areas on the anterior and inferior surfaces there were apparently discrete masses about two centimeters in diameter covered by a small amount of liver tissue so that the color was somewhat changed, but was not dense white. These were thought to be carcinomatous metastases of unknown origin. On making a section on the anterior surface near the lower margin, cysts began to roll out. Apparently it was a single cyst, but there rolled out over the operating room floor innumerable daughter cysts from one to five centimeters in diameter. Inasmuch as we had no protection of the abdominal cavity except a single pad to hold the intestines back, we placed a double rubber tube into the cavity, which was about four by five inches in diameter and surrounded it with gauze from the liver to the surface of the wound. The patient made a good postoperative recovery. We had not cleared out all the cysts, however, for they continued to come through the tubes for several days. She was discharged from the hospital in eight weeks with a small sinus discharging bile and it was about eleven months before the

wound healed. She was followed for three and a half years, during which time there was no evidence of abdominal implants.

Dr. Alfred Stillman operated last May upon a patient with echinococcus cyst of the liver. A Greek from Cyprus, 35 years old, in this country for 14 years, who had complained for four days of indigestion and epigastric pain. He was jaundiced, icteric index 25. The dye test of his gallbladder showed poor visualization and poor function. The preoperative diagnosis was cholecystitis and cholelithiasis. A cyst of the liver which practically divided the liver in two was found at operation just to the right of the suspensory ligament. After aspirating first clear and then bile-stained fluid, a daughter cyst appeared. An effort was made to extraperitonealize this area and the abdominal wound was partly closed around the gauze. At the second operation a week later the cyst was incised, evacuated and wiped dry. All the proper lining probably had been removed but owing to his lack of appreciation of just what this lining was an effort was made to separate another layer and soon he was involved in removing the entire adventitious sac and had almost accomplished this when a smart hemorrhage occurred. A large roll of packing was quickly and firmly inserted and the patient was sent back to the ward. After two transfusions he began to recover from shock and went along to slough the freed sac and close in the cavity left in the liver.

The reason for mentioning this case is because of the failure to recognize clearly what was true cyst lining and the nearly fatal result. The true lining is white, rather thin and separates out easily. The rest of the wall of the cyst is adventitious, produced by the tissue reaction to the cyst, its removal unnecessary for a cure and best left alone.

In another case, a young man, the diagnosis of echinococcus cyst of the liver was not made until some days after his gallbladder had been removed and daughter cysts were extruded alongside the drain. This patient died and autopsy showed a huge suppurating echinococcus cyst of the upper surface of the right lobe of the liver with a number of smaller cysts connecting with the bile ducts. He is sure that surgery could not have benefited this case even if the cyst could have been localized.

Dr. Allen O. Whipple thought that the approach to an echinococcus cyst was quite important from the standpoint of sequelae. Those who have had an opportunity to see a large amount of this work done in countries where it is endemic will appreciate what a real technic there is in connection with the removal of such a cyst. He thought Alessandri in Rome has done as much to describe it and the technic of removing it as anyone. One or two men in Australia have written on it but more from the point of view of its parasitology.

Five years ago he saw Alessandri remove several of these cysts. His technic was excellent. He averages from four to ten of these cases a month. His method of dealing with them when they are found initially is important, and has a great deal to do with the prevention of further spread. He empha-

sizes this because of the 23 echinococcus cysts that they have in their records at Presbyterian Hospital, two are exceedingly interesting. One of these is a Sicilian woman whom they know to have had echinococcus disease for 28 years. They have operated on her three times for recurrences, the last operation having been about six years ago. She now has another recurrence. The other case is a woman from Australia who was first operated on in San Francisco. She was pregnant at the time and was desperately ill. When she was delivered of her child it was thought she had twins for she still had an enormous abdomen that did not come down with the uterus. She was subsequently operated on and an echinococcus cyst was marsupialized. She remained well for seven years and then, when first seen by him, she had a large mass in the upper abdomen. They thought it was a recurrence of her liver cyst, but when he opened the peritoneum he found it was not in the liver but on the anterior wall of the stomach. It was very easy to peel away, and the woman remained well for four years. She then returned with what appeared to be a recurrence in the lower abdomen. On exploring her a cyst was found situated in the posterior fornix about 10 by 12 centimeters, and a second cyst beneath that, situated between the rectum and the vagina. These were removed intact. He does not doubt that this patient has other daughter cysts that will ultimately develop. The reason they recur is that this material was spilled out at the first operation.

In approaching these cysts, Alessandri brings out the point that if they can be approached before they are either infected or have become calcified, the chances of removing them are exceedingly good. Some of them—specially in two that he saw—the cyst was over the upper part of the dome of the right lobe. Alessandri makes an incision through the thin layer of liver tissue until he comes to the cyst wall, then he packs the area very carefully down to the line of incision with 1 per cent formalin gauze, aspirating a large part of the fluid contents, and injecting 1 per cent formalin, and after waiting a few minutes, aspirates again, applying traction to the wall of the cyst, as he aspirates, to separate it from liver tissue. As traction is applied he pushes with gentle sponge pressure and finally entirely removes the cyst intact. The cavity is temporarily packed with 1 per cent formalin which is taken out after it has been in for a few seconds. The rent is sewed up intact and the abdominal wall is closed without drainage. It certainly produces excellent results. Those cases that are infected or have calcified walls, he thinks, would have to be marsupialized, but if one bears in mind the possibility of removing them without marsupialization the possibility of recurrence will decrease.

Dr. Seward Erdman reported a case of echinococcus cyst seen in New York Hospital in 1930. A Turkish woman, 26 years of age, with a large tumor of the liver. Because of her nationality, and the presence of that smooth enlargement of the liver, it was thought to be an echinococcus cyst. The Alessandri method was employed in this case, using 2 per cent formalin

gauze for the packing. When they aspirated there were over 4,000 cubic centimeters of limpid, watery fluid in the cyst. The inside layer of an echinococcus cyst called the chitinous membrane has the consistency of the white of a hard boiled egg, though a little more dense and very brittle. They were able by very gently maneuvering this chitinous layer and with gentle employment of a sponge stick, to remove the cyst intact, which proved to be the size and somewhat of the consistency of a football bladder. It required the length of a long sponge stick to reach the bottom of the cavity in the liver after the cyst was removed. This cavity was lined with the leather-like, fibrous outer layer of the cyst formed by the host in reaction to the parasite, whereas the chitinous layer is developed by the parasite. An attempt was made to obliterate the cavity by suturing it; as a matter of fact he tried to remove part of it, but, as Doctor Stillman has said, one is apt to start bleeding or open up tiny bile ducts in the liver.

The woman left the hospital in six weeks and at that time the cavity held only two drams. However, the tiny sinus persisted for more than three months before healing. As he understood it, Doctor Cunniffe did not remove the chitinous layer of the sac; nevertheless, his case healed up before leaving the hospital. He had looked up the cases that they have had in New York Hospital and had found that those who recovered were apt to drain for quite a number of months. No scolices were found in the specimen. There was one daughter cyst. This would point to a chronic or burned-out process. If no scolices are present and no daughter cysts, perhaps it makes little difference where the fluid is spilled in the peritoneal cavity; however, it would be dangerous. Therefore one should carefully pad the wound with 2 per cent formalin gauze, to permit a more radical procedure than mere marsupialization, and to attain more rapid healing.

INTUSSUSCEPTION OF THE DESCENDING COLON

Dr. Edward R. Cunniffe presented a man 40 years of age. He had never been ill until May of this year when he began to pass bloody stools. There was no pain, no loss of weight, and no other symptoms. He was admitted to one of the Metropolitan hospitals and operated on for hemorrhoids in July, 1934. The rectal bleeding continued. Proctoscopic examination was negative.

When first seen by Doctor Cunniffe, August 29, he still complained of bleeding, to which was added abdominal pain which he had first noticed two weeks before, located well down in the rectum.

On physical examination a soft, freely movable mass was felt on the left side. It was not cystic in character nor painful. Rectal examination revealed a mass about 1.5 inches from the anal margin, occupying the central portion of the rectum which was dilated to double its size. The finger could be passed between the mass and the rectal wall. It was conical in shape.

Considering the history of bleeding which continued after the hemorrhoidectomy, the negative proctoscopic examination and the subsequent advent of pain with the appearance of a mass which could not be separated

entirely from the circumference of the bowel at that point, a diagnosis of intussusception of the descending colon—probably due to tumor—was made.

The patient was admitted to the Webb Avenue Hospital August 29, 1934, and operated on under general ether, nitrous-oxide and oxygen anesthesia. The abdomen was opened through a lower left rectal incision. The rectum and lower left colon were found to be very much dilated; extending up to the middle of the descending colon where collapsed bowel was found entering the intussusception. The intussusception was easily reduced by pressure from below upward, being readily accomplished up to the last inch or two where it could no longer be separated. A tumor could be felt within the wall of the intestine, and, realizing that this bowel had to be resected, no further attempt at reduction was made.

The bowel containing the intussusception and the tumor mass was removed by a modified Mikulicz operation, using the Rankin clamp. The upper blade of the clamp was removed after five days and the lower blade on the distal segment at the end of one week. The clamp that was placed on the spur was removed at the end of ten days, the spur was cut through and the continuity of the intestinal tract was readily established. The convalescence was satisfactory except that the wound had not closed completely. At the end of the fifth week this was closed under local anesthesia. The patient was discharged at the end of the eighth week.

Pathologic Report.—Examination revealed the tumor to be adenocarcinoma, Grade 3. The nodes that were examined were found to be clear.

The reason he shows this case is not on account of its rarity—it is the third he has met with and there must be a great many not reported, but because he is interested in the type of operation that should be employed in resections of the left colon. He has not used an immediate anastomosis in the left colon for a number of years, but has preferred to employ the Mikulicz two- or three-stage operation on account of the increased danger supposed to accompany the former procedure in this region. However, the Mikulicz operation has many drawbacks, not the least of which is prolonged hospitalization. This patient is well, he thinks, in as short a time as one could expect. He spent eight weeks in the hospital, and at least four weeks at home, making a total of three months' morbidity before returning to work. He is wondering if, with our modern and improved methods of preoperative preparation, one could not get just as satisfactory a result from either a side-to-side anastomosis or end-to-end anastomosis done immediately, with great shortening of the period of morbidity without increased risk.

Dr. Charles Gordon Heyd thought there were a number of interesting points presented by this case. The patient had an hemorrhoidectomy, and it has been their experience that about 20 per cent of the cases with sigmoidal tumors have had an hemorrhoidectomy before the exact nature of the condition has been determined. He is not thoroughly convinced what is the best procedure for colon tumors. Tumors of the right colon do not, as a rule, produce obstruction while those of the left colon tend to be complicated by some degree of obstruction. If obstruction exists, it is not, as a rule, complete, yet these patients suffer from some elements of chronic sickness. Before

any surgery is attempted they should invariably have preliminary cleansing of the bowel, dehydration should be corrected, measures to counteract the anemia, and deflation or decompression of the bowel should be obtained. Increasing experience has demonstrated the remarkable usefulness of a preliminary cecostomy as a means of meeting preoperative conditions. When complete obstruction does occur it is approximately ten to one that the obstruction will be in the left colon and a preliminary cecostomy is actually lifesaving.

He presumes few surgeons utilized the Mikulicz operation in the manner of its originator but prefers one or other of the many modifications. The Mikulicz operation must be reserved for a very definitely selected group of cases. In the presence of inflammation, or a thick fatty mesosigmoid, or in the very obese, it is very difficult to deliver the bowel sufficiently to do a satisfactory operation, and an imperfectly made Mikulicz operation with sloughing of the bowel loops and an infection of the anterior abdominal wall is a condition not to be lightly considered. Again, he thinks there is a tendency to underestimate the ultimate mortality of a Mikulicz operation. It has been his experience to have a few cases succumb from exhaustion during a prolonged convalescence. In other words, there is a delayed mortality following the Mikulicz operation that is usually not reported and is not considered when one speaks of the Mikulicz operation as being safe.

The graded obstructive operation as done by Doctor Cunniffe in this case and popularized by Rankin certainly met the technical condition in this patient. He is not inclined to believe, however, that the convalescence would have been materially shortened by doing a preliminary cecostomy.

Of great importance in the consideration of this subject is the fact that most of the patients with colonic neoplasms reach the surgeon for complications of the growth. He is convinced that irregular cramps and a change in bowel sensitivity are signs of extremely suspicious character. To wait for the diagnostic criteria of obstruction and hemorrhage is to encounter a relatively well-organized growth, while confirmatory roentgenographic evidence should be ordinarily sufficient to warrant an exploratory laparotomy. The element of intussusception in Doctor Cunniffe's case is interesting and some time ago he reported a case of carcinoma of the ileocecal region where the tumor acted as a spearhead producing a well-defined intussusception. The diagnosis of malignancy in that case was not made until the operation was performed.

Dr. John Douglas considered the subject very important, and one in which it is particularly difficult to lay down any hard and fast rules as to what should be done in every case. He was sorry to hear Doctor Heyd decry the Mikulicz operation for he had found it very valuable and, in his hands, particularly successful.

Of course, there must be some limitation of the cases on whom you are going to do a Mikulicz operation. If the patient comes in, in bad condition,

with obstruction, no doubt cecostomy should be done first and when the second stage is performed either a Mikulicz or, preferably, a resection by an aseptic end-to-end anastomosis. If the patient is in good condition with a moderate amount of distention when he comes in, if he is a patient whom you are able to get some gas through with only a partial obstruction, the Mikulicz operation is particularly valuable.

He did not think he had had, as a rule, anything near as long a period of morbidity as Doctor Cunniffe has mentioned. One of the most important reasons for this is getting a very long spur, even if you have to put the clamp on twice to crush it later, or else cut it through further with a cautery. Frequently you can close the colostomy and get a primary union even though you have feces coming out of the wound. You can then get your patient home in five or six weeks and he had occasionally sent cases home in considerably less time than that.

He thought aseptic resection could be done in a considerable number of cases, always with the idea that it is probably not perfectly aseptic, the peritoneum being able to take care of some infection. Again, in obese patients whom we see occasionally with a growth in the colon, the removal of a section of the sigmoid is not only especially difficult but these patients may, and do, sometimes die not from peritonitis, but from an infection of the abdominal wall. Therefore the suggested method of vaccination of the peritoneum is not going to do very much good to every case.

He preferred the Mikulicz or modified Mikulicz type of operation in the average sigmoid case, which certainly is not the Rankin method, where the Rankin clamp is used in doing his type of aseptic anastomosis. The modified Mikulicz is to make a good spur, remove the tumor, and leave two clamps on the abdominal wall just as long as you can, depending on the amount of postoperative distention, preferably 72 hours or occasionally 90 hours.

Dr. Allen O. Whipple asked Doctor Douglas if the patient is obstructed did he approve of cecostomy, and when the patient is deflated did he think there are advantages in doing an end-to-end or side-to-side anastomosis, and not the Mikulicz? If one does that in unfavorable, obstructed cases, why not in the favorable, those that are not obstructed but which, with a cecostomy, will go through with an end-to-end? Which cases did he reserve for the Mikulicz?

Doctor Douglas replied that in a certain number of cases where there is absolutely no obstruction and when you can completely empty the colon, an immediate end-to-end aseptic anastomosis might be preferable. He reserved for the Mikulicz operation those cases that come in with a certain amount of obstruction; he did not mean with much distention but those that you can keep in the hospital and possibly examine roentgenographically before operation. He had done the Mikulicz operation on cases in whom he had to open the colostomy within 36–48 hours, but such cases can usually wait 72 hours.

DOCTOR WHIPPLE asked if he thought one can remove as efficiently the gland-bearing area with a Mikulicz.

DOCTOR DOUGLAS said he did. The fact that had always surprised him is the small number of involved glands in so many of these cases. He thought one can usually get out a wedge and bring out a fairly good loop; often one can get as much with the Mikulicz as with an end-to-end anastomosis.

DOCTOR WHIPPLE said the only cases that he could remember in their series of colon carcinomata, as he recalled, in which they had recurrences in the abdominal wall, were those in which a Mikulicz had been done, and this number was astonishing, something like 30 per cent. As far as his own experience was concerned he believed where one can avoid a Mikulicz operation, cecostomy should be done and every effort should be made to do either an end-to-end or side-to-side anastomosis. His experience with the Mikulicz operation had been bad. They have had recurrences and bad sloughing infections in the abdominal wall, and, in a stout individual, the Mikulicz is especially difficult, although in thin individuals where one can bring out a good part of the bowel one has plenty of room to do a good anastomosis, he should like to register himself as against the Mikulicz.

DOCTOR DOUGLAS said that Dr. Richard Bolling, just before his death some six years ago, reviewed all of the cases of resection of the colon done during the previous 15 years at St. Luke's Hospital. This was before the aseptic method of resection was done as frequently as it is now. His paper was never published, but he showed so much lower mortality and improved morbidity and end results where the Mikulicz operation was done that it had the effect of strongly influencing all of the surgical staff of the hospital in favor of this type of operation.

PHYTOBEZOARS WITH GASTRIC ULCER*

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CASE REPORT.—A man of 42 was admitted to the Surgical Service B of the Episcopal Hospital on December 23, 1933, discharged January 27, 1934. The family history and previous medical history had no bearing on the present complaints. Two weeks before admission the patient ate a number of persimmons which were made particularly tasty by a thin coating of ice on the fruits. A few hours later he ate two "cannibal" sandwiches (raw hamburger steak) and drank some whiskey. At eight o'clock the same evening he began to have a heavy feeling in the stomach, followed by nausea and severe epigastric pain. From that day until admission he had a constant feeling of heaviness and nausea, or as he expressed it "turning of the stomach." Other than some tenderness in the right upper quadrant, the physical examination was negative. Six days after admission the roentgenologist reported a "large ulcer on lesser curvature which has possibly undergone malignant degeneration with infiltra-

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tion throughout distal half of stomach," and "the lesion has caused some obstruction." He had not been told about the persimmon feast. Gastric analysis showed an absence of free hydrochloric acid. The urine, the blood chemistry and the serologic examinations were negative.

At operation January 9, the stomach lumen, at the fundus, was found full of globular, putty-like masses which were easily moved from the fundus to the pylorus and back again. It was quite evident there was no carcinoma. An opening four inches long and parallel to the greater curvature was made on the anterior surface of the stomach. Through the opening all of the masses, eight in number, were expressed. The largest measured three inches in diameter, the next in size was two inches, a third was an inch and the five others were smaller. All of the masses were dry; dark in color, flecked with red spots, they resembled cooked meat balls. After the stomach was emptied, an inspection of the mucosa disclosed a saddle ulcer on the lesser curvature, each limb measuring two cm. The ulcer had a yellowish base and the edges were soft and smooth. The gastrotomy wound was closed and a posterior gastroenterostomy was performed.

On the seventh day the patient complained of nausea and a heavy feeling in the stomach. At this time gastric siphonage removed acrid, foul-smelling material and from that date convalescence was uninterrupted. On January 27, 18 days after the operation, the patient was discharged. Three months later he was seen in the End-Result Clinic and he then stated that he had been well except for a few attacks of nausea.

A history of a feast of persimmons followed in 24 hours by nausea and vomiting, and still later by recurring gastric upsets has always been noted in a few recorded cases of persimmon ball phytobezoars. When this triad of symptoms is present there is little excuse for an incorrect diagnosis. The case here reported had the typical history, yet he was diagnosed as a carcinoma of the stomach. It is hoped that the recording of this failure will refresh the memory and eliminate other mistakes in this rare stomach lesion. This patient was of added interest because the phytobezoars were complicated by a gastric ulcer, an association that has been noted in some of the other reports of persimmon ball. The relationship of the ulcer to the foreign body is undoubtedly one of irritation, but not by mechanical action alone. It is probable that the chemical action which precipitates the persimmon mass also causes a necrosis of the mucosa and the ulcer is aggravated by the pylorospasm excited by the foreign body.

PERFORATED CHYLOUS CYST OF THE MESENTERY*

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CYSTS of the mesentery are generally considered to be rare although each year a score or more cases are reported. The spontaneous perforation of such a cyst as occurred in the case being reported is unusual. The condition is of interest, not only because of its rarity but on account of the difficulty in diagnosing the true condition even at the operating table.

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We are concerned primarily with the complication of perforation and refer the reader to the excellent papers of Swartley[5] and of Timbal[6] for a discussion of mesenteric cysts in general. The earliest reported case of mesenteric cysts is that of Benevieni[5, 8] from an autopsy in 1507. From that time on, sporadic reports appeared until, in 1932, Warfield[7] estimated that there were probably 500 in all. Apparently the first successful operation should be credited to Tillaux[5, 8] (1880). Marsupialization was first done for this condition by Pean[5, 8] in 1883.

The manner in which the recognized varieties of mesenteric cysts should be classified has given rise to extensive discussion. Dowd[1] in a classical paper (after eliminating cysts due to echinococcus or malignant tumors) classifies the true embryonic or sequestration cysts according to the nature of their contents. Higgins and Lloyd[3] subsequently drew the distinction between cysts whose walls were of: (*a*) mesodermal origin, arising from remnants incarcerated behind the peritoneum and migrating forward between the leaves of the mesentery, and those of (*b*) intestinal origin, developing from a diverticulum or from persistent portions of the vitelline duct. In the former group, the tissue found in the wall is not differentiated into layers and the contents may be either serous, chylous, hemorrhagic or dermoid. As Warfield points out, the character of the cyst wall gives the only clue to its origin. The content of the cyst merely suggests accidental occurrences. Cysts occurring from embryonal rests of the intestinal wall reproduce in their structure the characteristic coats of the small bowel.

Rupture of a mesenteric cyst is mentioned as a possible complication, notably by Timbal.[6] There are relatively few records of this occurrence however. It was the cause of death in the early autopsy reports of Smith, Mery, LaFlaive and Walther.[6, 9] In the two latter cases severe exertion and strenuous purgation, respectively, were recognized as precipitating causes of the perforation. In 1883 Allbutt[6, 9] described an interesting case in which a mesenteric cyst perforated into the lumen of the bowel. The patient recovered. Shortly thereafter Menzies[6, 9] had a similar case. In both instances the diagnosis rested upon the history and the character of the fluid obtained by aspiration. There is every reason to believe, however, that this diagnosis was correct. So far as we can ascertain, our case of ruptured mesenteric cyst is the third to be found at operation. Previous reports are by Pederson[4] and Dutton.[2]

Pederson reported a case in a girl of seven. She had had intermittent abdominal pains for some time but no tumor had been observed. She fell, striking her abdomen. There was initial vomiting and thereafter increasing pain. On her admission the day after the injury, tenderness and rigidity were most marked in the left upper quadrant. The temperature was 103° and the pulse 138. At operation a whitish coagulum resembling curdled milk was found in the peritoneal cavity together with a tumor the size of a fist, attached to the mesentery of the small bowel. An uncomplicated recovery followed resection with end-to-end anastomosis of the bowel. The wall of the cyst showed no recognizable layers. It was composed of fibrous connective tissue

with an infiltration of round and plasma cells. This case should be classed as a chylous mesenteric cyst of mesodermal origin.

Dutton's patient was a 35-year-old woman who for two years had experienced occasional attacks of nausea and vomiting but no pain. Shortly after arising one morning, she experienced generalized abdominal cramps with vomiting. The abdomen was particularly tender in the right lower quadrant. The temperature was 99.2°, pulse 104, and leukocytes 12,500. At operation there was a thick, milky exudate with flaky scales on the peritoneal surfaces. A tumor the size of a grapefruit arose from the mesentery of the ileum about 18 inches above the ileocecal juncture. The ruptured cyst was aspirated and the wall marsupialized. The patient recovered. Examination of the cyst wall showed only chronic inflammatory tissue. This case can be classified as was that of Pederson's.

Case Report.—F. C., male, aged 34, was referred to the senior author by Dr. Frank Knight October 6, 1933. There had been no previous abdominal symptoms. The patient was awakened by a severe shooting pain in the upper abdomen followed by vomiting. This pain remained throughout the day, later shifting downward to the right of the umbilicus but no lower. The patient had taken a dose of magnesium citrate on the previous day. When seen 24 hours after onset, the temperature was 100.2°, pulse 120, respirations 28, blood pressure 144/100. Leukocytes were 17,600 and hemoglobin 100 per cent. He was acutely ill but not prostrated. The abdomen was scaphoid. There was distinct rigidity of the right rectus muscle, most pronounced opposite the umbilicus. No mass was palpable. Immediate laparotomy was determined upon with a provisional diagnosis of acute appendicitis, although an acute empyema of a low lying gallbladder could not be excluded.

Operation.—Under ether anesthesia, a high muscle splitting incision was made. As the peritoneum was opened turbid grayish green exudate escaped. This appeared to come from above and mesial to the cecum. The appendix was covered with the same exudate but presented no gross evidence of acute inflammation. Exploration disclosed a thick, white, creamy fluid coming down from above. A perforation in the upper right quadrant was suspected. A second incision was made through the upper right rectus. The stomach, duodenum and gallbladder were examined for perforation but nothing was found. On drawing up the great omentum a sudden gush of this same creamy fluid appeared in the wound. Exposure of the upper portion of the jejunum revealed a large tumor the size of a tennis ball situated in the mesentery. This tumor was indurated, acutely inflamed and had a perforation the size of a lead pencil from which this thick chylous fluid was exudating.

Excision was considered inadvisable owing to the extent of the lesion, its induration and congestion, and the proximity of large mesenteric vessels. Accordingly, the cyst was evacuated, a portion of its wall excised and the remainder marsupialized in the incision. A soft cigarette drain was left in the cavity. A large amount of exudate was aspirated from the pelvis and a drain placed in this region, being brought out through the first incision. An additional drain was placed outside the cecum. Both incisions were then closed in layers about the drains.

Culture of the peritoneal exudate showed no bacterial growth. The pathologist reported that the fragments of cyst wall consisted of fibrous tissue with inflammatory changes. There was no differentiation of this tissue into layers and no muscle fibers were seen. It was apparently a chylous cyst of mesodermal origin similar to the two other cases described.

The patient's convalescence was without incident. The temperature

reached a peak of 102° on the second day and subsided to normal on the fifth day. A leukocytosis of 11,000–17,000 persisted for about 12 days. The cigarette drain in the cyst cavity was shortened on the 12th day and removed completely four days later. The patient was discharged 24 days after operation. At this time the drainage tracts were all filled with clean granulation tissue. Eleven months after operation the patient is entirely recovered, having a good abdominal wound and no symptoms.

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NEUROGENIC SARCOMA*

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Philadelphia, Pa.

Case I.—Mrs. M. M., aged 63, was admitted to Misericordia Hospital January 27, 1934, with a tumor measuring one-half inch in diameter, on the posterior aspect of the right thigh, in its middle third. The tumor appeared two months before admission, and was first noticed as a small, hard swelling, about the size of a marble, just under the skin. Three weeks before admission she noted that the swelling had increased in size, and bled easily. Her past medical history was negative. The family history showed no evidence of malignancy. Her physical examination was generally negative, except for this swelling on the posterior surface of the thigh, which now appeared as a growth about one-half inch in diameter, with a small necrotic area on its most prominent portion. There was a mild degree of inflammatory reaction around the growth. Laboratory findings, including blood chemistry, were within normal limits, with the exception of a slight secondary anemia. A wide excision of the tumor was made. The pathologic diagnosis was given as "sarcoma—probably neurogenic type" (Figs. 1 and 2). She was readmitted to the hospital March 22, 1934, with a large mass in the right inguinal region, which was completely excised and diagnosed as metastatic sarcoma. In the period between her first and second admissions she was given intensive roentgen ray therapy over the site of the primary tumor, the right inguinal region, and the chest, in addition to gradually increasing doses of Coley's fluid, until March 19, 1934. These injections were discontinued after two months because of the patient's poor condition; at this time she was complaining of violent pains in the anterior portion of the chest, marked dyspnea, and tachycardia. Numerous attacks of chest pain occurred, which were diagnosed as emboli. She died June 9, 1934. The period of life, therefore, from the time that this patient first noticed the growth was about eight months.

Case II.—Miss S. T., aged 28, was admitted to Misericordia Hospital

* Presented before the Philadelphia Academy of Surgery, October 1, 1934.

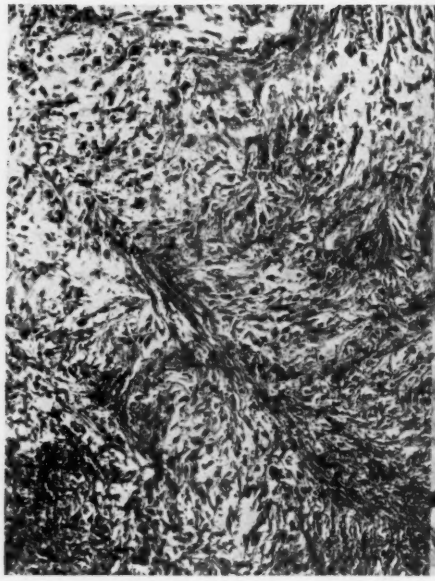

FIG. 1.—(Case I.) Neurogenic sarcoma. Illustrating arrangement of spindle cells in bundle formations; marked cellularity, scantiness of connective tissue stroma (×92).

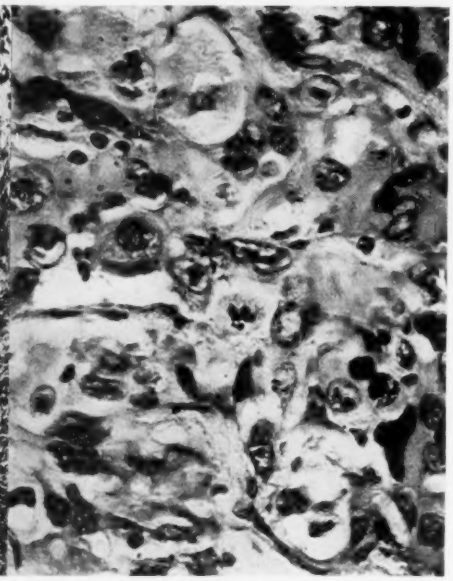

FIG. 2.—(Case I.) Neurogenic sarcoma. Illustrating the classic cytologic features of rapid growth (×625).

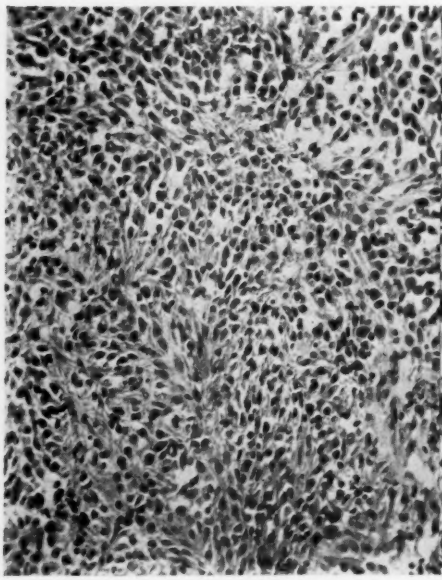

FIG. 3.—(Case II.) Neurogenic sarcoma (×200).

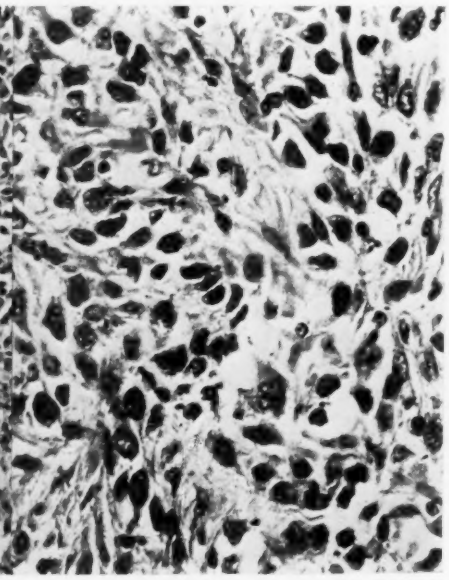

FIG. 4.—(Case II.) Neurogenic sarcoma (×560).

December 10, 1931, complaining of a hard, freely movable tumor over the anterior aspect of the right thigh, in the region of the apex of Scarpa's triangle. She had noticed this tumor about three months prior to her admission, but one month before it had gradually increased in size and the uppermost portion of the tumor became red in color. The tumor was freely movable, and not painful. It was widely excised, and pathologic examination reported it to be a "spindle cell sarcoma" (Figs. 3 and 4). A review of this section revealed it to be a sarcoma of probably the neurogenic type. The Wassermann reaction was negative. The laboratory examinations, including blood chemistry, were within normal limits. Deep roentgen ray therapy was immediately instituted over the site of the primary tumor, the right inguinal region, and the chest. She was also given gradually increasing doses of Coley's fluid.

April 26, 1932, she was again admitted to the hospital, with numerous nodules in the inguinal region, the chest, and the scalp. Roentgen ray examination of the chest revealed numerous metastatic nodules in both lungs, but there was no roentgenographic evidence of metastases in any of the bones. April 30, 1932, a small growth was removed from the scalp, for diagnosis, and revealed it to be similar to the one removed from the thigh. The patient died in August, 1932. The span of life in this case, from the onset of the development of the tumor, was about eleven months.

Doctor Ryan's purpose in reporting these two cases of neurogenic sarcoma was to emphasize the importance of pathologic diagnosis in small superficial tumors—the growth in each of these cases might easily have been excised in the office, and no thought be given to their grave malignant nature—as well as to show the inefficacy of excision, roentgen ray, and Coley's fluid, in their treatment. In discussing the treatment of neurogenic sarcoma, at the Memorial Hospital, Stewart and Copeland, in their monograph on this subject which appeared in the American Journal of Cancer for July, 1931, vol. 15, p. 1235, make the following comments:

"The results of amputation are impressive.

"(1) Zinc chloride paste occasionally gives a surprisingly good result.

"(2) Interstitial irradiation with radon implants has been almost uniformly disappointing.

"(3) External radiation has given a few good results in low grade tumors; however, it has been very disappointing in the high grades of malignancy.

"(4) It is their opinion that the dosage of external radiation is too small. The best result occurred in a case in which sloughing was produced."

And summarize as follows:

"(1) After excision recurrence is the rule. These are not recurrences in the ordinary sense, but are new tumors arising from nerves in the vicinity.

"(2) Definite evidence that irradiation after excision prevents or delays recurrence is lacking, although the five year regression of certain tumors suggests that this is at least probable.

"(3) There is little to support irradiation in the more malignant types.
"(4) Many patients have been apparently made worse by treatment.
"(5) No patient in Group II or III has lived for five years without the disease and without any treatment during the five year period, except patients treated by amputation."

Dr. A. R. Camero said that these tumors were not very large. They were more or less freely movable and not attached to overlying skin nor underlying bone. They were definitely tumors of the subcutaneous tissues or soft parts, and as Stewart and Copeland pointed out have been often classified under the general headings of fibrosarcoma and spindle cell sarcoma. The term spindle cell sarcoma, while it indicates the shape of the predominant cell in the tumor, applies to many various subdivisions of sarcoma, each of which may have a different origin, clinical course, prognosis; and each of which may respond differently to various forms of treatment. While it is not always easy to subdivide the spindle cell sarcomas into more specific subgroups for a more complete diagnosis, it is always desirable for the pathologist, whenever possible, to give a specific sarcoma diagnosis and not to be content with classification under the general heading of spindle cell sarcoma.

The question arises regarding the best form of treatment in similar cases of neurogenic sarcoma. It is obvious that the answer to this question will not be forthcoming until pathologists are able to diagnose specifically the various forms of spindle cell sarcomas, thus enabling the surgeon to follow up carefully the different varieties and to evaluate the various forms of treatment used in the specific types of tumors. Even a perfect follow up system will be worthless in evaluation of forms of treatment if all of these tumors be grouped under the general heading of spindle cell sarcoma.

The so called carcinoid tumors are benign tumors and are rather frequently found in the appendix and along the intestinal tract. They take the silver stain and have therefore been called argentaffinomas. The sections reported were ordinary hematoxylix-eosin preparations. The reporter knows of no specific stain which will help in the diagnosis of neurogenic sarcoma. The diagnosis is based on the characteristic histologic appearance of the tumor, chiefly on the arrangement and shape of the cells. When amputations are done and the specimens carefully dissected, a definite nerve connection has been demonstrated in a small number of cases, but this is not necessary for diagnosis.

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INDEX TO VOLUME 101

A

Abdominal Cavity, Draining of, in Peritonitis, 662.
Abdominal Pain, Acute, 438.
Abdominal-wall Infections, 997.
Abducent and Facial Nerves in Brain Tumor, 329.
Abscess, Brain, 190; Ophthalmic Symptoms in, 56; Surgical Management of, 7.
Abscess, Intracranial, Osteomyelitis of Skull with, 1286; Mediastinal, in an Infant, 802; Solitary, of Liver, 933.
Adenoma of Islet Cells with Hyperinsulinism, 1209.
ADLER, FRANCIS HEED: Physiology of Disease of Optic Nerve, 3.
Adrenal Lesions, Intestinal Ulceration in, 554.
ADSON, ALFRED W.: Surgical Management of Brain Abscess, 7.
Aged, Hyperthyroidism in the, 1181.
ALEXANDER, JOHN: Total Pulmonary Lobectomy and Pneumonectomy, 393.
Alimentation, Jejunal, Jejunostomy with, 708.
ALPERS, BERNARD J.: Cerebral Osteochondroma of Dural Origin, 27.
ALTMAN, RAPHAEL: Appendices Found as Contents of Femoral Herniae, 1270.
AMENDOLA, FREDERICK H.: Acute Intestinal Obstruction, 1250.
Amniotic Fluid, 529.
Amoebic Ulceration of Rectum Simulating Carcinoma, 799.
AMREICH, J.: Operative Surgery, Review of, 974.
Analgesia, Spinal, 690.
ANDERSON, ROGER: Ambulatory Method of Treating Fractures of Patella, 1082.
Anesthesia, Brachial Plexus Block, 1153; Spinal, Use and Abuse of, 702.
Aneurysm, Subclavian, 568.
Aneurysmorrhaphy, 944.
Ankle-bone Block for Paralytic Drop Foot, 1091.
ANSPACH, BROOKE M.: Gynecology by, Review of, 976.
Anuria, Unilateral, in Bladder Malignancy, 603.
Aphasia in Brain Tumors, 373.
APPEL, KENNETH E.: Post-encephalitic Personality, 44.
Appendices Found as Contents of Femoral Herniae, 1270.
Appendicitis, Acute, Fibrinopurulent Peritonitis Following, 1123; Acute Tuberculous, 740.
Applied Anatomy by Gwilym G. Davis, Revised by George P. Muller, Review of, 976.
Arteriography in Gangrene of Extremities, 766.
Artery, Central, of Retina, Occlusion of, 318.
Arthroplasty of Elbow, 793.
AVERBUKH, S. S.: Access to Sphenopalatine Ganglion and Second Branch Trifacial Nerve, 819.
Avulsion of Epiphysis of Iliac Crest, 1078.

B

BABBITT, JAMES A.: Surgery in Chronic Middle-ear Infection, 407.
BANCROFT, FREDERIC W.: Bilateral Transplantation of Ureters, 1128; for Exstrophy of Bladder, Jejunal Ulcer Following Gastric Resection, 1125.
BARRINGER, BENJAMIN S.: Radium Treatment of Cancer of Bladder, 1425.
BEER, EDWIN: Surgery of Bladder Tumors, 1412.
BEHNEY, CHARLES AUGUSTUS: Sympathectomy for Pain in Pelvic Carcinoma, 411.
Benign Encapsulated Tumors of Lateral Ventricle by Walter E. Dandy, Review of, 977.
BERNHEIM, ALICE R.: Parathyroidectomy for Raynaud's Disease and Scleroderma, 1012.
BERRY, GORDON: Psychology of Deafness, 38.
BICK, EDGAR M.: Fibrosarcoma of Extremities, 759.
Biliary System after Cholecystectomy, 921.
Biliary Tract, Surgery of, Mortality in, 460.
Bladder, Carcinoma of the, 1407; Diathermy for Carcinoma of, 1418; Exstrophy of, Bilateral Transplantation of Ureters for, 1128; External Irradiation of Cancer of, 1428; Malignancy, Unilateral Anuria in, 603; Radium Treatment for Cancer of, 1425; Total Cystectomy for Cancer of, 1415; Tumors, Surgery of, 1412; Upper Urinary Tract in Carcinoma of, 1432.

Bleeding Gastric and Duodenal Ulcer, 1377.
Block, Ankle-bone, for Paralytic Drop Foot, 1091.
Blood Transfusion Apparatus, Improved, 813.
Bond, Earl D.: Post-encephalitic Personality, 44.
Bone Pathology, Tumors of Parathyroid and Associated, 1275.
Bothe, Albert E.: Neurocytoma of Kidney, 418.
Bothe, Frederick A.: Hyperthyroidism Associated with Pregnancy, 422.
Braasch, William F.: Diathermy for Carcinoma of Bladder, 1418.
Brachial Plexus Block Anesthesia, 1153.
Brain, Abscess, 7; 190; Ophthalmic Symptoms in, 56; Lesions and Duodenal Ulcers, 156; Tumor, Facial and Abducent Nerves in, 329; Tumors, Aphasia in, 373.
Breast, Cystic Disease of the, 1144.
Breitmann, M. G.: Draining of Abdominal Cavity in Peritonitis, 662.
Brevda, I. S.: Access to Sphenopalatine Ganglion and Second Branch of Trifacial Nerve, 819.
Brown, Henry P., Jr.: Arthroplasty of Elbow, 793.
Burns, Plastic Surgery in, Due to Roentgen Rays and Radium, 979.

C

Cadman, Rev. Dr. S. Parkes: Eulogy of Lewis Stephen Pilcher, 659.
Camero, A. R.: Neurogenic Sarcoma, 1455.
Campbell, Edward H.: Sphenopalatine Ganglion, 429.
Cancer of Bladder, External Irradiation of, 1428; Radium Treatment for, 1425; Total Cystectomy for, 1415.
Cancer-Gastric Ulcer Problem, 536.
Cantor, Meyer O.: Lugol's Solution in Acute Secondary Parotitis, 1171.
Carabba, Victor: Herniorrhaphy Using Living Flap, 1264.
Carcinoma of the Bladder, 1407; Diathermy for, 1418; Upper Urinary Tract in, 1432.
Carcinoma, Pelvic, Sympathectomy for Pain in, 411; Primary, of Duodenum, 961; Primary, of Liver, 613; of Rectum, Amebic Ulceration Simulating, 799; of Stomach, Operability of, 1200.
Carcinomas of Large Bowel, Part 1, Colon, 863; Part 2, Rectum, 1042.
Cardia of Stomach, Malignant Polypoid Tumors of, 839.
Cardiac Failure, Total Thyroidectomy for, 1276; Improvement Following Gallbladder Surgery, 478.
Carmody, M. G.: Lymphosarcoma of Stomach, 1136.
Cataract Operations, Psychosis after, 313.
Caulk, John R.: Upper Urinary Tract in Carcinoma of Bladder, 1432.
Causalgia, Treatment of, by Thoracic Sympathetic Ganglionectomy, 222.
Cave, Henry W.: Amebic Ulceration of Rectum Simulating Carcinoma, 799.
Cavum Septi Pellucidi and Cavum Vergae, 269.
Cecum, Diastasic Perforation of Normal, 1257.
Central Artery of Retina, Occlusion of, 318.
Cerebellum, Benign Cysts of, 347.
Cerebral Osteochondroma of Dural Origin, 27; Thrombosis, Hypotension in, 296; Trauma, Dehydration Treatment of, 76.
Children, Acute Empyema in, 617; Decerebrate Rigidity in, 338.
Cholecystectomy, Biliary System after, 921; and Splenectomy, 951.
Cholecystitis, Acute, 902.
Cholecystoduodenal Fistula, 958.
Choledochus Cyst, 912; Dilatation of, in Relation to Cholecystitis and Cholecystectomy, 599.
Chylothorax, Rupture of Thoracic Duct with, 1367.
Chylous Cyst, Perforated, of Mesentery, 1452.
Cleft-palate Surgery, Push-back Operation in, 445.
Clute, Howard M.: Hyperthyroidism in the Aged, 1181.
Cobb, Stanley: Lingual Spasm, 49.
Coley, William B.: Malignant Tumor of Synovial Membrane of Knee-joint, 805.
Coller, Frederick A.: Intraperitoneal Vaccination in Surgery of Colon, 886.
Colon, Descending, Mobilization of, 971; Intraperitoneal Vaccination, in Surgery of, 886; Intussusception of Descending, 1447.
Comroe, Bernard I.: Non-surgical Causes of Acute Abdominal Pain, 438.
Counseller, Virgil S.: Diathermy for Carcinoma of Bladder, 1418.
in Brain Abscess, 56.
Cowan, Alfred: Ophthalmic Symptoms
Craig, Winchell McK.: Surgical Management of Brain Abscess, 7.
Crawford, Baxter L.: Leiomyoma of Small Intestine, 726.
Crossan, Edward T.: Phytobezoars with Gastric Ulcer, 1451.

CUNNIFFE, EDWARD R.: Double Echinococcus Cyst of Liver, 1442; Intussusception of Descending Colon, 1447.
Cutaneous Distribution of Trigeminal Nerve, 212.
Cyst, Choledochus, 912; Double Echinococcus, of Liver, 1442; Mesenteric, 1289; Pancreatic, 786; Perforated Chylous, of Mesentery, 1452.
Cystectomy, Total, for Cancer of Bladder, 1415.
Cystic Disease of the Breast, 1144.
Cystine Nephrolithiasis, 746.
Cystoscopy and Urography, 1101.
Cysts, Benign, of Cerebellum, 347; Pilonidal, 469; Solitary, of the Kidney, 1279.

D

DANDY, WALTER E.: Benign Encapsulated Tumors of Lateral Ventricle, by, Review of, 977.
DAVIS, GWILYM G.: Applied Anatomy by, Review of, 976.
Deafness, Psychology of, 38.
DEAN, ARCHIE L., JR.: External Irradiation of Bladder Cancer, 1428.
Decerebrate Rigidity in Children, 338.
Deformities of Sella Turcica, 201.
Dehydration Treatment of Cerebral Trauma, 76.
DENNIS, FREDERICK SHEPARD: Memoir, 1297.
Descending Colon, Mobilization of, 971.
DESCHWEINITZ, G. E.: Relation of Ophthalmology and Other Departments at the University Hospital, 64.
DETARNOWSKY, GEORGE: Surgical Treatment of Chronic Pancreatitis, 1342.
Diastasic Perforation of Normal Cecum, 1257.
Diathermy for Carcinoma of Bladder, 1418.
Dilatation of Choledochus in Relation to Cholecystitis and Cholecystectomy, 599.
Diseases, Common Southern, 572.
Dislocation, Complicated, 633.
Diverticulum of Esophagus, 935.
DIXON, CLAUDE F.: Mobilization of Descending Colon, 973.
DORRANCE, GEORGE M.: Push-back Operation in Cleft-palate Surgery, 445.
DRISSEN, EDWARD M.: Acute Tuberculous Appendicitis, 740.
Drop Foot, Paralytic, Ankle-Bone Block for, 1091.
Duodenal Ulcers, and Brain Lesions, 156; and Gastric, Bleeding, 1377.
Duodenum, Primary Carcinoma of, 961.

E

EASTON, EDWARD R.: Gas Gangrene, 1393.
Echinococcus, Double, Cyst of Liver, 1442.
ECKEL, JOHN L.: Acute Purulent Meningitis, 383.
EGGERS, CARL: Diverticulum of Esophagus, 935; Resection Thoracic Portion Esophagus for Chronic Ulcer, 940; Solitary Abscess of Liver, 933.
EISENBERG, A. A.: Neurofibroma of Hypoglossal Nerve, 834.
EISS, STANLEY: Biliary System after Cholecystectomy, 921.
Elbow, Arthroplasty of, 793.
ELIASON, ELDRIDGE L.: Mortality in Surgery of Biliary Tract, 460; Perforated Chylous Cyst of Mesentery, 1452.
ELIOT, ELLSWORTH, JR.: Gas Gangrene, 1393; Memoir of Frederick Shepard Dennis, 1297.
Empyema, Acute, in Children, 617; Recurrent, Thoracis, 559.
Encephalitis Lethargica, 303.
Epilepsy, Meningioma as Cause of, 167.
Epiphysis of Iliac Crest, Avulsion of, 1078.
ERB, WILLAM H.: Mortality in Surgery of Biliary Tract, 460; Superior Laryngeal Nerve and Superior Pole in Thyroidectomies, 1353.
ERDMANN, JOHN F.: Malignancy of the Gallbladder, 1139.
Esophagectomy, Thoracic, 940.
Esophagus, Diverticulum of, 935.
Eulogy of Lewis Stephen Pilcher, 659.
Exstrophy of Bladder, Bilateral Transplantation of Ureters for, 1128.
External Condyle of Humerus, Fracture of, in Children, 1069.
Extremities, Arteriography in Gangrene of, 766; Fibrosarcoma of, 759.

F

Facial and Abducent Nerves in Brain Tumor, 329.
FARR, CHARLES E.: Meckel's Diverticulum, 1026; Mediastinal Abscess in an Infant, 802.
Fascial Flap, Living, Herniorrhaphy Using, 1264.
FAY, TEMPLE: Dehydration Treatment of Cerebral Trauma, 76.
Femoral Herniae, Appendices Found as Contents of, 1270.
Femur, Fracture of, 801; Malunited Subtrochanteric Fracture of, 1294.
FERGUSON, LEWIS K.: Pilonidal Cysts, 469.
Fibrinopurulent Peritonitis Following Acute Appendicitis, 1123.
Fibromyositis, Chronic Generalized, 237.
Fibrosarcoma of Extremities, 759.

Fistula, Acquired Renocolic, 1291; Cholecystoduodenal, 958; Salivary, Treatment of, by Irradiation, 1175.
FITZ-HUGH, THOMAS, JR.: Cardiac Improvement Following Gallbladder Surgery, 478.
Fluid, Amniotic, 529.
Formation of Gallstones, 624.
FOX, G. W.: Rupture of Thoracic Duct with Chylothorax, 1367.
Fracture of External Condyle of Humerus in Children, 1069; of Femur, 801; Malunited Subtrochanteric, 1294.
Fractures, Compressed, of the Vertebrae, 776; of Patella, 1082.
FRANTZ, VIRGINIA K.: Adenoma of Islet Cells with Hyperinsulinism, 1299.
FRAZIER, CHARLES H.: Chronic Subdural Hematoma, 671; End-results of Thyroid Surgery, 1195; Superior Laryngeal Nerve and Superior Pole in Thyroidectomies, 1353.
FREEMAN, NORMAN E.: Hemorrhage in Relation to Shock, 484.
FREEMAN, WALTER: Motor and Sensory Overlap in Spinal Roots, 133.
FRIEDMAN, LOUIS: Neurofibroma of Hypoglossal Nerve, 834.
FULTON, JOHN F.: Effect of Lesions of Hypothalamus on Gastro-intestinal Tract and Heart in Monkeys, 363.

G

Gallbladder, Intraperitoneal Rupture of, 950; Malignancy of the, 1139; Surgery, Cardiac Improvement Following, 478.
Gallstones, Formation of, 624.
Ganglion, Sphenopalatine, Access to, 429, 819.
Ganglionectomy, Thoracic Sympathetic, 222.
Ganglioneuroma, Mediastinal, 827; of Mediastinum, 1282.
Gangrene of Extremities, Arteriography in, 766; Gas, 1393; and Torsion of Portion of Lesser Omentum, 1117.
GARDNER, W. JAMES: Intracranial Operations in the Sitting Position, 138.
GARLOCK, JOHN H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, 1012.
Gas Gangrene, 1393; Clinical, with Absence of Welch Bacillus, 817.
Gastric and Duodenal Ulcer, Bleeding, 1377; Hernia, Diaphragmatic, with Callous Ulcer, 1113; Resection, Jejunal Ulcer Following, 1125; Ulcer-Cancer Problem, 536; Phytobezoars with, 1451.
Gastro-enterostomy, Jejunal Ulcer Following, 1111.
GILLIES, SIR HAROLD D.: Plastic Surgery in Burns Due to Roentgen Rays and Radium, 979.
GLASER, MARK ALBERT: Sensory Root Tumors of Trigeminal Nerve, 146.
Glossopharyngeal Neuralgia, 256.
Glucose, Action of, on Emptying of Stomach, 500.
Goiter, Surgical Treatment of Toxic, 1358.
GOODE, JOHN V.: Skin Grafting, 927.
GRANT, FRANCIS C.: Brain Lesions and Duodenal Ulcers, 156.
GRINNELL, ROBERT S.: Omentopexy in Portal Cirrhosis of Liver, 891.
GROFF, ROBERT A.: Meningioma as Cause of Epilepsy, 167.
Growth Centers, Osteochondritis of, 1062.
Gynecology, by Brooke M. Anspach, Review of, 976.

H

HARBIN, LESTER: Primary Carcinoma of Duodenum, 961.
HARBIN, W. P.: Primary Carcinoma of Duodenum, 961.
HARBIN, W. P., JR.: Primary Carcinoma of Duodenum, 961.
HECK, FRANK J.: Bleeding Malignant Polypoid Tumors in Cardia of Stomach, 839.
Hematoma, Chronic Subdural, 671.
Hematuria, Essential, 647.
Hemianopsia, Frank, The Occurrence of, 176.
Hemorrhage, Massive, in Peptic Ulcer, 856; in Obstructive Jaundice, 605; in Relation to Shock, 484.
HERMAN, LEON: Cystine Nephrolithiasis, 746.
Hernia, Diaphragmatic Gastric, with Callous Ulcer, 1113; Incisional, Treatment by Flaps of Anterior Sheath of Rectus, 754; Inguinal, Peritoneum in Repair of, 550.
Herniae, Femoral, Appendices Found as Contents of, 1270.
Herniorrhaphy Using Living Fascial Flap, 1264.
HERZMARK, MAURICE H.: Malunited Subtrochanteric Fracture of Femur, 1294.
HEYL, JAMES HARRY: Fracture of External Condyle of Humerus in Children, 1069.
HINTON, J. WILLIAM: Massive Hemorrhage in Peptic Ulcer, 856.
HIRSCH, SIDNEY: Improved Blood Transfusion Apparatus, 813.
HODES, PHILIP J.: Dilatations of Cavum Septi Pellucidi and Cavum Vergae, 269.

Holloway, T. B.: Occurrence of Frank Hemianopsia, 176.
Horseshoe Kidney with Stone, 1441.
Hour-glass Stomach, 969.
Humerus, Fracture of External Condyle of, in Children, 1069.
Hunt, Verne C.: Operability of Carcinoma of Stomach, 1200.
Hunter, Doctor William, of Newport, 506.
Hyperinsulinism, Adenoma of Islet Cells with, 1299; Subtotal Pancreatectomy for, 1336.
Hyperthyroidism in the Aged, 1181; Associated with Pregnancy, 422.
Hypoglossal Nerve, Neurofibroma of, 834.
Hypotension in Cerebral Thrombosis, 296.
Hypothalamus, Lesions of the, Effect of, on Gastro-intestinal Tract and Heart in Monkeys, 363.

I

Iliac Crest, Avulsion of Epiphysis of, 1078.
Incisional Hernia, 754.
Infant, Mediastinal Abscess in an, 802.
Infection, Middle Ear, Surgery in Chronic, 407.
Infections, Abdominal Wall, 997.
Ingham, Samuel D.: Structure of the Neuraxis in Voluntary and Reflex Movements, 184.
Inguinal Hernia, Peritoneum in Repair of, 550.
Intestinal Obstruction, Acute, 1250; Ulceration in Adrenal Lesions, 554.
Intestine, Leiomyoma of Small, 726; Submucous Lipomas of, 734.
Intracranial Operations in Sitting Position, 138; Tumors, 246.
Intraperitoneal Rupture of Gallbladder, 950; Vaccination in Surgery of Colon, 886.
Intussusception of Descending Colon, 1447.
Irradiation, External, of Bladder Cancer, 1428; Treatment of Salivary Fistula by, 1175.

J

Jaundice, Obstructive, Hemorrhage in, 605.
Jejunal Ulcer Following Gastric Resection, 1125; Following Gastro-enterostomy, 1111; Primary, 1110; Primary Perforated, 1225.
Jejunostomy with Jejunal Alimentation, 708.
Jenkins, William H.: Hour-glass Stomach, 969.
Jennings, John E.: A Retrospect and an Appreciation of Franklin H. Martin, 979A.
Johnson, Julian: Effect of Superior Laryngeal Nerves on Tracheal Mucus, 494; End-results of Thyroid Surgery, 1195.
Johnston, C. G.: Action of Glucose on Emptying of Stomach, 500.
Jones, Thomas E.: Lymphosarcoma of Stomach, 1136.

K

Kidney, Horseshoe, with Stone, 1441; Neurocytoma of, 418; Solitary Cysts of the, 1279.
King, Joseph E. J.: Brain Abscess, 190.
King, Orville C.: Spinal Analgesia, 690.
Kirschbaum, J. D.: Submucous Lipomas of Intestine as Cause of Intestinal Obstruction, 734.
Kleinberg, Samuel: Avulsion of Epiphysis of Iliac Crest, 1078.
Klingenstein, Percy: Cystic Disease of the Breast, 1144.
Klopp, Edward J.: Leiomyoma of Small Intestine, 726.
Knee-joint, Malignant Tumor of Synovial Membrane of, 805.
Knox, Harry E.: Cholecystoduodenal Fistula, 958.
Kornblum, Karl: Deformities of Sella Turcica by Tumors of Pituitary Fossa, 201.
Kraus, Walter M.: Cutaneous Distribution of Trigeminal Nerve, 212.
Krumbhaar, E. B.: Doctor William Hunter of Newport, 506.
Kwan, S. T.: Treatment of Causalgia by Thoracic Sympathetic Ganglionectomy, 222.

L

Lacey, James T.: Amniotic Fluid, 529.
Landon, Lyndon Holt: Gastric Ulcer-Cancer Problem, 536.
Large Bowel, Carcinoma of, Part 1, Colon, 863; Rectum, Carcinomas of, 1042.
Larson, Lawrence M.: Mesenteric Cyst, 1289.
Laryngeal Nerves, Superior, Effect of, on Tracheal Mucus, 494; and Superior Pole in Thyroidectomies, 1353.
Lee, A. B.: Cystoscopy and Urography, 1101.
Lee, Walter E.: Cystine Nephrolithiasis, 746.
Leiomyoma of Small Intestine, 726.
Leithauser, Daniel J.: Lugol's Solution in Acute Secondary Parotitis, 1171.
Lemmon, William T.: Malignant Neoplasm of the Thyroid, 1190.

Lesions, Brain, and Duodenal Ulcers, 156; of the Hypothalamus, Effect of, on Gastro-intestinal Tract and Heart in Monkeys, 363.
Lesser Omentum, Torsion and Gangrene of, 1117.
Lethargica, Encephalitis, 303.
LEVERING, J. WALTER: Peritoneum in Repair of Inguinal Hernia, 550.
LILLIE, O. R.: Rupture of Thoracic Duct with Chylothorax, 1367.
Lingual Spasm, 49.
Lipomas, Submucous, of Intestine, 734.
LIPSHUTZ, BENJAMIN: Acute Cholecystitis, 902.
Liver Abscess, Solitary, 933; Double Echinococcus Cyst of, 1442; Omentopexy in Portal Cirrhosis of, 891; Primary Carcinoma of, 613.
Lobectomy, Total Pulmonary, and Pneumonectomy, 393.
LOWENBERG, K.: Unclassified Organic Psychosis, 357.
LUBOTSKY, D. N.: Access to Sphenopalatine Ganglion and Second Branch of Trifacial Nerve, 819.
Lugol's Solution in Acute Secondary Parotitis, 1171.
LYLE, H. H. M.: Applied Anatomy by Gwilym G. Davis, Revised by George P. Muller, Reviewed by, 976.
Lymphogranuloma Inguinale, Stricture of Rectum from, 1284.
Lymphosarcoma of Stomach, 1136.

M

MAIER, HERBERT C.: Clinical Gas Gangrene with Abscess of Welch Bacillus, 817.
Malignancy of Gallbladder, 1139; Unilateral Anuria in Bladder, 603.
Malignant Neoplasm of Thyroid, 1190; Polypoid Tumors in Cardia of Stomach, 839.
MANHEIMS, PERRY J.: Clinical Gas Gangrene with Absence of Welch Bacillus, 817.
Martin, Franklin H.: A. Retrospect and an Appreciation of, 979A.
MATTHEWS, WARREN B.: Peptic Ulcers Greater Curvature of Stomach, 844.
MAZZOLA, VINCENT P.: Gynecology, by Brooke M. Anspach, Review of, by, 976.
MCCAUGHAN, JOHN M.: Subtotal Pancreatectomy for Hyperinsulinism, 1336.
MEFETRIDGE, ELIZABETH M.: Arteriography in Gangrene of Extremities, 766.
MCINDOE, A. H.: Plastic Surgery in Burns Due to Roentgen Rays and Radium, 979.
MCLAUGHLIN, CHARLES W.: Intestinal Ulceration in Adrenal Lesions, 554.
MCNEER, GORDON: Sarcoma of Stomach, 1206.
MEADE, RICHARD H.: Recurrent Empyema Thoracis, 559.
MEADE, RICHARD H., JR.: Intraperitoneal Rupture Gallbladder, 950.
Meckel's Diverticulum, 1026; Attached to Root of Mesentery, 1125.
Mediastinal Abscess in an Infant, 802; Ganglioneuroma, 827; Tumors, 788.
Mediastinum, Ganglioneuroma of, 1282.
MELENEY, FRANK L.: Zinc Peroxide in Abdominal Wall Infections, 997.
Meningioma as Cause of Epilepsy, 167.
Meningitis, Acute Purulent, 383.
MEREDITH, J. M.: Selection of Pituitary Cases for Surgery, 228.
Mesenteric Cyst, 1289.
Mesentery, Meckel's Diverticulum Attached to Root of, 1125; Perforated Chylous Cyst of, 1452.
Middle Ear Infection, Surgery in Chronic, 407.
MIXTER, W. JASON: Lingual Spasm, 49.
Modified "T" Tube, 816.
Monkeys, Lesions of Hypothalamus, Effect of, on Gastro-intestinal Tract and Heart in, 363.
MORRISON, P. J.: Hemorrhage in Obstructive Jaundice, 605.
MORRISON, R. B.: Dilatation of Choledochus in relation to Cholecystitis and Cholecystectomy, 599.
Mortality in Surgery of Biliary Tract, 460.
Motor and Sensory Overlap in Spinal Roots, 133.
MULLER, GEORGE P.: Applied Anatomy by Gwilym G. Davis, Revised by, Review of, 976; Subclavian Aneurysm, 568.
MUSSER, J. H.: Social and Economic Implications of Three Common Southern Diseases, 572.

N

Nephrolithiasis, Cystine, 746.
Nerve, Physiology of Disease of Optic, 3.
NEUHOF, HAROLD: Aneurysmorrhaphy, 944; Pericardiectomy for Adhesive Pericardium, 946.
Neuralgia, Glossopharyngeal, 256.
Neuraxis, Structure of, in Voluntary and Reflex Movements, 184.
Neurocytoma of Kidney, 418.
Neurofibroma of Hypoglossal Nerve, 834.
Neurogenic Sarcoma, 1455.

New York Surgical Society, Meeting of, February 14, 1934, 779; April 25, 1934, 799; May 9, 1934, 933; Oct. 10, 1934, 1110; Oct. 24, 1934, 1123; Nov. 28, 1934, 1279.
NORDLAND, MARTIN: Mesenteric Cyst, 1289.
NORTH, JOHN PAUL: Perforated Chylous Cyst of Mesentery, 1452; Splenectomy and Cholecystectomy, 951; Use and Abuse of Spinal Anesthesia, 702.

O

Obliterans, Thrombo-Angiitis, in Women, 324.
Obstruction, Acute Intestinal, 1250; Intestinal, Submucous Lipomas of Intestine, as the Cause of, 734.
Occlusion of Central Artery of Retina, 318.
O'CROWLEY, C. RUTHERFORD: Carcinoma of the Bladder, 1407.
Omentopexy in Portal Cirrhosis of Liver, 891.
Operative Gynecology, by H. V. Peham, and J. Amreich, Review of, 974.
Ophthalmic Symptoms in Brain Abscess, 56.
Ophthalmology, Relation of, and Other Departments, 64.
Optic Canals, Erosion of, in Study of Intracranial Tumors, 246; Nerve, Physiology of Disease of, 3.
Organic Psychosis, Unclassified, 357.
ORNSTEEN, A. M.: Chronic Generalized Fibromyositis, 237.
ORR, THOMAS G.: A Modified "T" Tube, 816.
OSMOND, L. H.: Deformities of Sella Turcica by Tumors of Pituitary Fossa, 201.
Osteochondritis of Growth Centers, 1062.
Osteochondroma, Cerebral, of Dural Origin, 27.
Osteomyelitis of Skull with Intracranial Abscess, 1286.
OVERHOLT, RICHARD H.: Thoracoplasty for Pulmonary Tuberculosis, 576.
OVERTON, LEWIS M.: Osteochondritis of Growth Centers, 1062.
OWEN, HUBLEY R.: Mediastinal Tumors, 788; Pancreatic Cyst, 786; Splenectomy and Cholecystectomy, 951.

P

PACK, GEORGE T.: Sarcoma of Stomach, 1206.
Pain, Non-surgical Causes of Acute Abdominal, 328.
PANCOAST, HENRY K.: Roentgen Diagnostic Significance of Erosion of Optic Canals in Study of Intracranial Tumors, 246.
Pancreas, Adenoma of, 1299.
Pancreatectomy for Hyperinsulinism, 1336.
Pancreatic Cyst, 786.
Pancreatitis, Surgical Treatment of Chronic, 1342.
Paralysis, Bilateral, of Facial and Abducent Nerves in Brain Tumors, 329.
Paralytic Drop Foot, Ankle-Bone Block for, 1091.
Parathyroid, Tumors of, and Associated Bone Pathology, 1275.
Parathyroidectomy for Raynaud's Disease and Scleroderma, 1012.
Parotitis, Lugol's Solution in Acute Secondary, 1171.
Patella, Fractures of, 1982.
PATTERSON, HOWARD A.: Osteomyelitis of Skull with Intracranial Abscess, 1286.
PEET, MAX MINOR: Glossopharyngeal Neuralgia, 256.
PEHAM, H. V.: Operative Surgery, Review of, 974.
PELOUZE, P. S.: Pseudomembranous Trigonitis, 594.
Pelvic Carcinoma, Sympathectomy for Pain in, 411.
PENDERGRASS, EUGENE P.: Dilatations of Cavum Septi Pellucidi and Cavum Vergae, 269.
PENKE, MADELINE: Meckel's Diverticulum, 1026.
PENNOYER, GRANT P.: Rhinophyma, 1283.
PEPPER, O. H. PERRY: Hypotension in Cerebral Thrombosis, 296.
Peptic Ulcer, Massive Hemorrhage in, 856; Ulcers Greater Curvature of Stomach, 844.
Perforated Jejunal Ulcer, Primary, 1225.
Perforation, Diastasic, of Normal Cecum, 1257.
Pericardium, Adhesive, Pericardiectomy for, 946.
Peritoneum in Repair of Inguinal Hernia, 550.
Peritonitis, Draining of Abdominal Cavity in, 662; Fibrinopurulent, Following Acute Appendicitis, 1123.
Personality, Post-encephalitic, 44.
Philadelphia Academy of Surgery, Feb. 14, 1934, 779; April 2, 1934, 950; May 7, 1934, 1274.
Physiology of Disease of Optic Nerve, 3.
Phytobezoars with Gastric Ulcer, 1451.
Pilcher, Lewis Stephen, Eulogy of, 659.
Pilonidal Cysts, 469.
Pituitary Cases for Surgery, 228; Fossa, Deformities of Sella Turcica by Tumors of, 201.

Plastic Surgery in Burns Due to Roentgen Rays and Radium, 979.
Pneumonectomy, Total Pulmonary Lobectomy and, 393.
Polypoid Tumors, Malignant, in Cardia of Stomach, 839.
Portal Cirrhosis of Liver, Omentopexy in, 891.
PORTMANN, U. V.: Treatment of Salivary Fistula by Irradiation, 1175.
Post-encephalitic Personality, 44.
Posterior Fossa, Sensory Root Tumors of Trigeminal Nerve Arising from, 146.
POTTER, EUGENE B.: Intraperitoneal Vaccination in Surgery of Colon, 886.
POTTER, PHILIP C.: Fibrinopurulent Peritonitis Following Acute Appendicitis, 1123; Meckel's Diverticulum Attached to Root of Mesentery, 1125.
Pregnancy, Hyperthyroidism Associated with, 422.
PRIESTLEY, JAMES T.: Bleeding Malignant Polypoid Tumors in Cardia of Stomach, 839; Essential Hematuria, 647.
Prolapse of Rectum, Surgical Treatment of, 1051.
Pseudomembranous Trigonitis, 594.
Psychology of Deafness, 38.
Psychosis after Cataract Operations, 313; Unclassified Organic, 357.
PUESTOW, C. B.: Dilatation of Choledochus in Relation to Cholecystitis and Cholecystectomy, 599.
Pulmonary Lobectomy, Total, and Pneumonectomy, 393; Tuberculosis, Thoracoplasty for, 576.
Purulent Meningitis, Acute, 383.
Push-back Operation in Cleft-palate Surgery, 445.
Pyelo-ureteroplasty for Stricture, 1441.

Q

QUINBY, WILLIAM C.: Total Cystectomy for Cancer of Bladder, 1415.

R

Radium and Roentgen Rays, Plastic Surgery in Burns Due to, 979; Treatment of Cancer of Bladder, 1425.
RAIFORD, THEODORE S.: Carcinomas of Large Bowel, Part I, Colon, 863; Carcinomas of Large Bowel, Rectum, Part II, 1042.
Rammstedt Operation, Modified, 965.
RANDALL, ALEXANDER: Unilateral Anuria in Bladder Malignancy, 603.
RAVDIN, I. S.: Action of Glucose on Emptying of Stomach, 500; Hemorrhage in Obstructive Jaundice, 605.
Raynaud's Disease and Scleroderma, Parathyroidectomy for, 1012.
Rectal Prolapse, Surgical Treatment of, 1051.
Rectum, Amebic Ulceration of, Simulating Carcinoma, 799; Large Bowel, Carcinomas of, 1042; Stricture of, from Lymphogranuloma Inguinale, 1284.
Rectus, Treatment of Incisional Hernia by Flaps of Anterior Sheath of, 754.
Renocolic Fistula, Acquired, 1291.
Retina, Occlusion of Central Artery of, 318.
Rhinophyma, 1283.
RHODES, GEORGE K.: Diastasic Perforation of Normal Cecum, 1257.
RHONE, THOMAS B.: Brachial Plexus Block Anesthesia, 1153.
RIABOFF, PETER JOHN: Acquired Renocolic Fistula, 1291.
RIEGEL, CECILIA: Hemorrhage in Obstructive Jaundice, 605.
RIESMAN, DAVID: Encephalitis Lethargica, 303.
Rigidity, Decerebrate, in Children, 338.
ROBERTSON, JARRATT P: Cystoscopy and Urography, 1101.
Roentgen Rays and Radium, Plastic Surgery in Burns Due to, 979.
ROTHSCHILD, NORMAN S.: Treament of Incisional Hernia by Flaps of Anterior Sheath of Rectus, 754.
Rupture of Normal Spleen, 1389; of Thoracic Duct with Chylothorax, 1367.
RUSSELL, ETHEL C.: Psychosis after Cataract Operations, 313.
RUSSELL, JAMES I.: Ganglioneuroma of Mediastinum, 1282; Solitary Cysts of the Kidney, 1279.
RYAN, THOMAS: Neurogenic Sarcoma, 1455.

S

SAELTZER, DUDLEY V.: Diastasic Perforation of Normal Cecum, 1257.
SAGER, W. WARREN: Hour-glass Stomach, 969.
SALEEBY, ELI: Malignant Neoplasm of the Thyroid, 1190.
Salivary Fistula, Treatment of, by Irradiation, 1175.
SALVIN, ARTHUR A.: Surgical Treatment of Rectal Prolapse, 1051.
Sarcoma, Neurogenic, 1455; of Stomach, 1206.
SARMA, P. JOSEPH: Surgical Treatment of Chronic Pancreatitis, 1342.
SAUER, PAUL K.: Horseshoe Kidney with Stone, 1441; Pyelo-ureteroplasty for Stricture, 1441.
SCARLETT, HUNTER: Occlusion of Central Artery of Retina, 318.

SCHNABEL, TRUMAN G.: Primary Carcinoma of Liver, 613.
Scleroderma and Raynaud's Disease, Parathroidectomy for, 1012.
Sella Turcica, Deformities of the, 201.
SEMENOVA, O. S.: Access to Sphenopalatine Ganglion and Second Branch of Trifacial Nerve, 819.
Sensory and Motor Overlap in Spinal Roots, 133; Root Tumors of Trigeminal Nerve, 146.
Septi Pellucidi, Cavum and Cavum Vergae, 269.
SHAFIROFF, BENJAMIN G. P.: An Instrument for Skin Graft, 814.
SHALLOW, THOMAS A.: Malignant Neoplasm of the Thyroid, 1190; Tumors of Parathyroid and Associated Bone Pathology, 1275.
SHARPE, WILLIAM: Benign Encapsulated Tumors of Lateral Ventricle, by Walter E. Dandy, Review by, 977.
SHAWAN, HAROLD K.: Appendices Found as Contents of Femoral Herniae, 1270.
Shock, Hemorrhage in Relation to, 484.
SILBERT, SAMUEL: Thrombo-angiitis Obliterans in Women, 324.
Sitting Position, Intracranial Operations in the, 138.
Skin Graft, An Instrument for, 814; Grafting, 927.
Skull, Osteomyelitis of, with Intracranial Abscess, 1286.
Small Intestine, Leiomyoma of, 726.
SMITH, BEVERLY C.: Jejunal Ulcer Following Gastro-enterostomy, 1111; Primary Jejunal Ulcer, 1110; Primary Perforated Jejunal Ulcer, 1225.
SMITH, MORRIS K.: Surgical Treatment of Toxic Goiter, 1358.
SOPHIAN, LAWRENCE: Mediastinal Ganglioneuroma, 827.
Southern Diseases, Common, 572.
Spasm, Lingual, 49.
Sphenopalatine Ganglion, 429; Access to, 819.
SPILLER, WILLIAM G.: Bilateral Paralysis of Facial and Abducent Nerves in Brain Tumors, 329.
Spinal Analgesia, 690; Anesthesia, Use and Abuse of, 702; Roots, Motor and Sensory Overlap in, 133.
Spleen, Spontaneous Rupture of Normal, 1389.
Splenectomy and Cholecystectomy, 951.
STEINKE, CARL R.: Acute Empyema in Children, 617.
STETTEN, DEWITT: Diaphragmatic Gastric Hernia with Callous Ulcer, 1113; Torsion and Gangrene of Lesser Omentum, 1117.
STILLMAN, ALFRED: Stricture of Rectum from Lymphogranuloma Inguinale, 1284.
Stomach, Action of Glucose on Emptying of, 500; Cardia of, Malignant Polypoid Tumors of, 839; Hour-glass, 969; Lymphosarcoma of, 1136; Operability of Carcinoma of the Stomach, 1200; Peptic Ulcers, Greater Curvature of, 844; Sarcoma of, 1206.
Stone, Horshoe Kidney with, 1441.
Stricture, Pyelo-ureteroplasty for, 1441; of Rectum from Lymphogranuloma Inguinale, 1284.
Structure of the Neuraxis in Voluntary and Reflex Movements, 184.
Subclavian Aneurysm, 568.
Subdural, Chronic, Hematoma, 671.
Submucous Lipomas of Intestine, 734.
Subtrochanteric Fracture of Femur, Malunited, 1294.
Superior Larygeal Nerves, Effect of, on Tracheal Mucus, 494; Pole in Thyroidectomies and Superior Laryngeal Nerve, 1353.
Surgery, End-results of Thyroid, 1195; Selection of Pituitary Cases for, 228.
Surgical Treatment of Chronic Pancreatitis, 1342.
SWARTLEY, WILLIAM B.: Choledochus Cyst with Double Common Bile Duct, 912.
SWEET, JOSHUA E.: Formation of Gallstones, 624.
SWINTON, NEIL W.; Hyperthyroidism in the Aged, 1181.
Sympathectomy for Pain in Pelvic Carcinoma 411.
Sympathetic Ganglionectomy, Thoracic, 222.
Synovial Membrane of Knee-joint, Malignant Tumor of, 805.

T

"T" Tube, Modified, 816.
THOMAS, T. TURNER: Complicated Dislocations, 633.
Thoracic Duct, Rupture of, with Chylothorax, 1367; Esophagectomy, 940; Sympathetic Ganglionectomy, 222.
Thoracis, Recurrent Empyema, 559.
Thoracoplasty for Pulmonary Tuberculosis, 576.
THORPE, EDWARD S.: Decerebrate Rigidity in Children, 338.
Thrombo-angiitis Obliterans in Women, 324.
Thrombosis, Cerebral, Hypotension in, 296.
Thyroid, Malignant Neoplasm of the, 1190; Surgery, End-results of, 1195.
Thyroidectomies, Superior Pole in, and Superior Laryngeal Nerve, 1353.

Thyroidectomy, Total, for Cardiac Failure, 1276.
Torsion and Gangrene of Portion of Lesser Omentum, 1117.
Toxic Goiter, Surgical Treatment of, 1358.
Tracheal Mucus, Effect of Superior Laryngeal Nerves on, 494.
Trauma, Cerebral, Dehydration Treatment of, 76
Trifacial Nerve, Access to Sphenopalatine Ganglion and Second Branch of, 819.
Trigeminal Nerve, Distribution of, 212; Sensory Root Tumors of, 146.
Trigonitis, Pseudomembranous, 594.
Tuberculosis, Pulmonary, Thoracoplasty for, 576.
Tuberculous Appendicitis, Acute, 740.
Tumor, Brain, Facial and Abducent Nerves in, 329; Malignant, of Synovial Membrane of Knee-joint, 805.
Tumors, Aphasia in Brain, 373; Intracranial, 246; Malignant Polypoid, in Cardia of Stomach, 839; Mediastinal, 788; of Parathyroid and Associated Bone Pathology, 1275; of Pituitary Fossa, Deformities of Sella Turcica, by, 201; Sensory Root, of Trigeminal Nerve, 146; Surgery of Bladder, 1412.

U

Ulcer, Bleeding Gastric and Duodenal Ulcer, 1377; Gastric-Cancer Problem, 536; Gastric, Phytobezoars with, 1451; Jejunal, Following Gastric Resection, 1125; Massive Hemorrhage in Peptic, 586; Primary Jejunal, 1110; Primary Perforated Jejunal, 1225.
Ulceration, Amebic, of the Rectum, Simulating Carcinoma, 799; Intestinal, in Adrenal Lesions, 554.
Ulcers, Duodenal, and Brain Lesions, 156; Peptic, Greater Curvature of Stomach, 844.
Unilateral Anuria in Bladder Malignancy, 603.
University Hospital, Relation of Ophthalmology and Other Departments, 64.
Ureters, Bilateral Transplantation of, for Exstrophy of Bladder, 1128.
Urinary Tract, Upper, in Carcinoma of Bladder, 1432.
Urography and Cystoscopy, 1101.

V

Vaccination, Intraperitoneal, in Surgery of Colon, 886.
Vasiliu, Demitrie O.: Benign Cysts of Cerebellum, 347.
Veal, J. Ross: Arteriography in Gangrene of Extremities, 766.
Vergae, Cavum and Cavum Septi Pellucidi, 269.
Vertebrae, Compressed Fractures of the, 776.

W

Wadhams, Robert P.: Herniorrhaphy Using Living Flap, 1264.
Waggoner, R. W.: Unclassified Organic Psychosis, 357.
Wagner, Lewis Clark: Ankle-bone block for Paralytic Drop Foot, 1091.
Walscheid, Arthur J.: Review of Operative Surgery by, 974.
Watts, James W.: Effect of Lesions of Hypothalamus on Gastro-intestinal tract and Heart in Monkeys, 363.
Weeder, S. Dana: Choledochus Cyst with Double Common Bile Duct, 912.
Weisenberg, Theodore H.: Aphasia in Brain Tumors, 373.
Welch Bacillus, Clinical Gas Gangrene with Absence of, 817.
Wentworth, H. A.: Occurrence of Frank Hemianopsia, 176.
Westermann, John J.: Bleeding Gastric and Duodenal Ulcer, 1377.
Whaley, James H., Jr.: Biliary System after Cholecystectomy, 921.
Whipple, Allen O.: Adenoma of Islet Cells with Hyperinsulinism, 1209.
Wilbur, Dwight L.: Essential Hematuria, 647.
Willard, DeForest P.: Compressed Fractures of the Vertebrae, 776.
Winkelman, N. W.: Acute Purulent Meningitis, 383.
Wolfer, John A.: Jejunostomy with Jejunal Alimentation, 708.
Wolferth, Charles C.: Cardiac Improvement Following Gallbladder Surgery, 478; Total Thyroidectomy for Cardiac Failure, 1276.
Wolfson, William L.: Modified Rammstedt Operation, 965.
Women, Thrombo-angiitis Obliterans in, 324.

Y

Young, Ralph H.: Spontaneous Rupture of Normal Spleen, 1389.
Zinc Peroxide in Treatment of Microaerophilic and Anaerobic Infections, 997.

Z

Zollinger, Robert: Acute Tuberculous Appendicitis, 740.

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Complete Table of Contents pages 2 and 4

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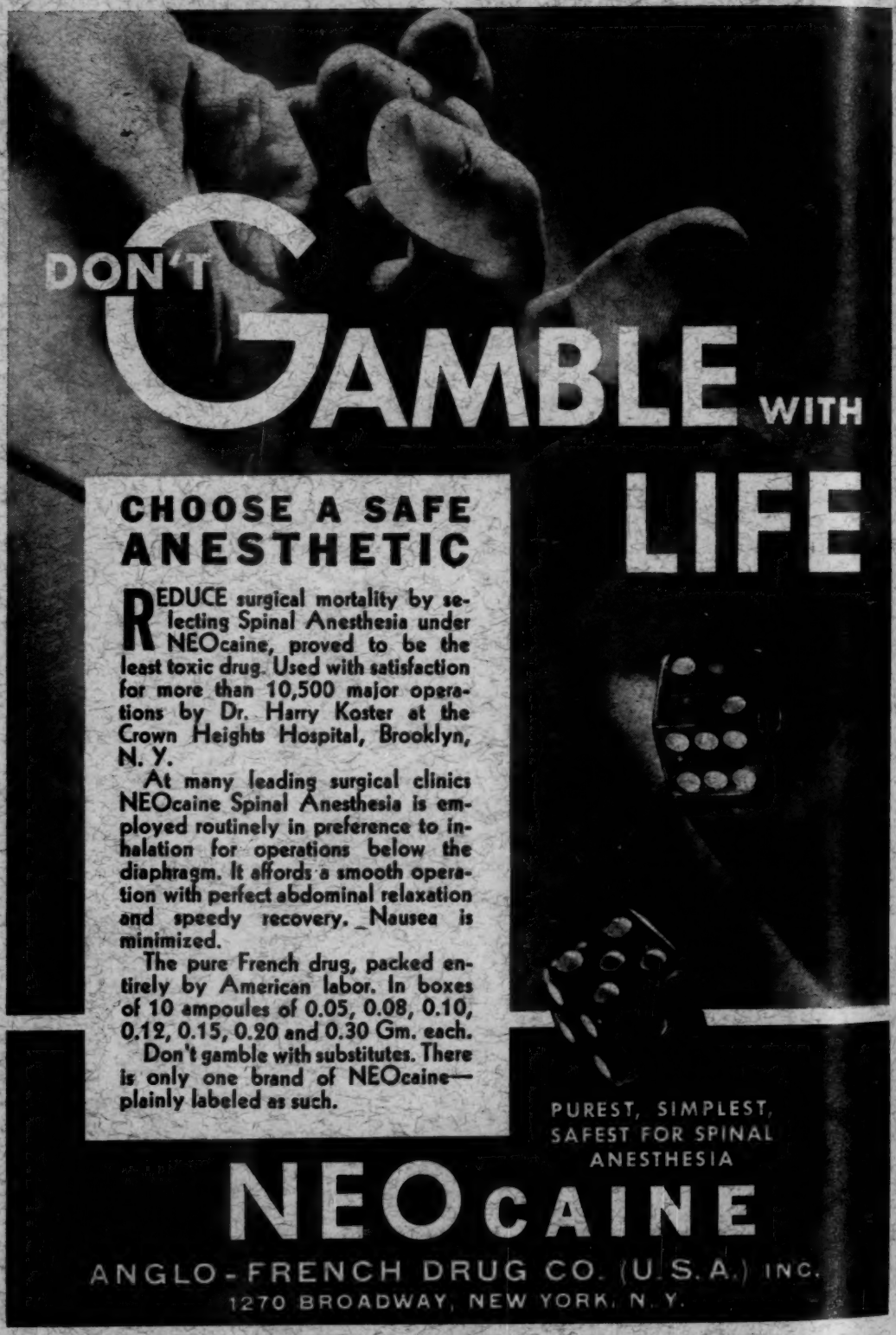
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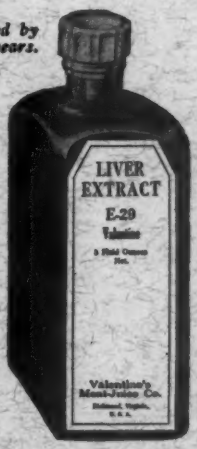

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